BLOOD SUPPLY SAFETY

HEARING

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON
ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

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BLOOD SUPPLY SAFETY

FRIDAY, JULY 13, 1990

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 11:20 a.m., in room 2123, Rayburn House Office Building, Hon. John D. Dingell (chairman) presiding.

Mr. DINGELL. The subcommittee will come to order.

This morning, the subcommittee commences the second of a series of hearings on the safety of the blood supply of this Nation. This inquiry has its roots in the early to mid-1980's, when the blood industry and the Government failed to prevent transfusion of thousands of pints of blood and blood products infected with the AIDS virus. Today, however, our focus is on the present and not on the past, and this investigation will be directed towards answering the question of whether the blood supply is as safe as it could be or as it should be and to also ascertain what it is that we should do to assure that the best possible steps are taken to assure safety of all persons involved in this very important human activity.

On this point, there is good news and there is bad news. The blood supply appears safer today than ever. In March of 1985, the first direct screening test for AIDS became generally available, an enhanced test for hepatitis B was finally instituted in 1987, and testing for hepatitis C began earlier this year. Despite the historic fears of the blood industry and some Federal officials, all of this has been accomplished without creating any national shortages of blood.

The bad news is that the American Red Cross, which collects over half of all the whole blood in the United States has had serious and persistent problems with its procedures for testing and keeping track of this blood. According to inspection reports by the Food and Drug Administration and the Red Cross's own internal reports, various Red Cross collection centers have released infected blood, mixed up records, violated AIDS testing procedures, and failed to deter infected or undesirable donors. Moreover, the unprecedented FDA inspection of the Red Cross National Headquarters, which was completed on May 25 of this year, found that the Red Cross blood-collection centers were not even complying with the Red Cross's own standard operating procedures, this in apparent violation of the September 1988 agreement between the Red Cross and the Food and Drug Administration.

The subcommittee and the American people will want to know whether other collectors of whole blood or producers of blood products suffer from the same deficiencies as the Red Cross. On this score, the subcommittee will depend on the skill and dedication of FDA inspectors. I am heartened by the work that the FDA's field inspectors have done in this area in recent years, even though the Chair has continuously had to be critical of the inadequacy of resources, personnel, and money available to Food and Drug in carrying out its responsibilities.

Ultimately, this investigation will attempt to determine whether the attitude of the blood bankers and the capability of the Federal regulators have changed enough as a result of the AIDS debacle and that both can respond quickly and effectively when the next infectious agent surfaces in the blood supply. To help us begin this assessment, our first panel consists of recognized and respected experts in the field of AIDS treatment, blood banking, and hemophilia. All are quite familiar with the response to the AIDS epidemic, and the Chair looks forward to their very important testimony.

Some other comments, I think, are appropriate at this time, before we commence our proceeding.

On July 10, the American Red Cross issued a press release that states that the public can take assurance from the fact that only six cases of transfusion AIDS have been reported since the testing and screening have been instituted, according to the Centers for Disease Control in Atlanta. Notwithstanding the problems that the Red Cross has experienced in keeping track of donors and units of blood after they have been tested, which will be explored today, the Red Cross statement was somewhat startling to the committee.

The CDC monthly HIV/AIDS report shows that, so far this year, 76 people have been added to the list of transfusion AIDS cases each month. Why the disparity? We will inquire into it.

The committee requested clarification of this matter immediately from the CDC, which was provided. The CDC explained that the discrepancy between the large number of newly-reported cases and the small number of confirmed cases since the AIDS screening test was instituted in March 1985 is explained by two factors.

First, the average incubation period for transfusion recipients between infection and diagnosis of AIDS is about 7 years. Second, patients are not reportable to the CDC until they develop AIDS. Thus, it is obvious that the actual number of transfusion AIDS cases since the screening test became available will not be known for some time. CDC is currently aware of 11 such cases, almost double the number cited in the Red Cross press release.

No one disputes the fact that the AIDS screening test has made the blood supply enormously safer than it was prior to 1985. The point of our inquiry is—and I want to make it clear—to find whether the blood industry, including the American Red Cross as an important constituent thereof, is doing everything that it can to make the blood supply as safe as it ought to be.

Statements which are made on this matter will only be helpful if they are made responsibly and if they are made factually and if they contribute to an intelligent discussion of what it is that needs to be done to assure that this Nation has the safest and the best

blood supply for the protection of all persons involved in and dependent upon that industry.

It appears that this will be one of the things which the committee will have to address, and the Chair wants to make it plain that one of our purposes would be to see to it that this discussion in the committee and elsewhere is conducted responsibly, with great attention not only to fact but also to the best way in which the matter should be addressed.

The letter from the Center for Disease Control will be inserted into the record at this point.

[The letter follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES,
PUBLIC HEALTH SERVICE,
CENTERS FOR DISEASE CONTROL,
Atlanta, GA, July 12, 1990.

HON. JOHN DINGELL, *Chairman*
Committee on Energy and Commerce,
U.S. House of Representatives,
Washington, D.C.

DEAR MR. CHAIRMAN: This is in response to the request by Robin Flowers of your staff for clarification regarding the transmission of human immunodeficiency virus (HIV) via blood transfusions and the reporting of cases of acquired immunodeficiency syndrome (AIDS) associated with transfusions.

HIV infection is a progressive disease process, with severe immunosuppression and AIDS as its clinical endpoint. Persons infected with HIV can remain asymptomatic for years before developing clinical illness and AIDS. For transfusion recipients, the average incubation period between infection with HIV and a diagnosis of AIDS has been estimated to be about 7 years. Patients are not reportable to CDC until they develop AIDS.

Transfusion of HIV-infected blood is a highly efficient mode of transmission of HIV; more than 95 percent of persons who are exposed to HIV through blood transfusions became infected. Fortunately, the deferral of donors at high risk since March 1983 and the routine screening of blood and plasma donors initiated in March 1985 have greatly reduced the risk of new infections from receipt of transfusions.

AIDS cases were first reported among transfusion recipients in 1982. By May 31, 1990, a total of 3,425 transfusion-associated AIDS cases had been reported to the Centers for Disease Control (CDC). However, given the long period between infection with HIV and diagnosis of AIDS, cases of AIDS from the pool of persons infected prior to donor screening (1985) will continue to occur for years.

A CDC spokesman was quoted in the July 11 issue of The Washington Times as saying, "Only 11 of those cases were diagnosed after screening for the AIDS virus began in March 1985. . . ." To clarify that information, it is necessary to distinguish between all reported transfusion-associated AIDS cases and those cases that resulted from transfusions of screened blood. Despite routine donor deferral and screening of donated blood since 1985, a small risk of HIV infection remains for recipients of blood screened as negative for HIV antibody. CDC estimated in 1988 that the risk of transmission of HIV via a blood transfusion screened as negative for HIV antibody is approximately 1 in 40,000 transfused units. In 1989, the American Red Cross made an even lower estimate of 1 in 153,000. The rare new transfusion-associated HIV infections occur when donors are tested soon after they are infected but before the development of detectable antibody. Of the persons infected with HIV as a result of transfusion of blood screened since 1985, 11 have developed AIDS (as of May 31, 1990).

The information quoted in The Washington Times would more accurately read as follows:

> According to the Centers for Disease Control, 3,425 cases of AIDS resulting from infected blood have been reported since 1981. Investigation of AIDS cases who received blood transfusions after screening began in March 1985 has identified only 11 who were infected from these transfusions.

The figure of 11 transfusion-associated AIDS cases resulting from screened blood is a meaningful statistic. These are confirmed AIDS cases for whom a seropositive donor was identified upon repeat donation or testing.

For all AIDS cases, CDC estimates completeness of reporting to be between 70 percent and 90 percent. We are unaware of any problems that would create a disproportionate percentage of underreporting of transfusion-associated cases.

I hope this information is helpful in clarifying the comments published in The Washington Times.

Sincerely,

WILLIAM L. ROPER, M.D., M.P.H.,
Director.

Mr. DINGELL. The Chair recognizes the distinguished gentleman from Virginia, Mr. Bliley, for an opening statement.

Mr. BLILEY. Thank you, Mr. Chairman.

I commend you for calling this hearing to begin this subcommittee's examination of the safety of the Nation's blood supply. I understand this is the first of a series of public hearings on this important, indeed life-or-death issue.

The safety of the blood supply should be one of paramount concern by the medical community, by the so-called blood industry, those who collect and sell blood and blood products, and by those who regulate the industry. But is it or was it back in 1983, when the Centers for Disease Control warnings that we would have a disaster on our hands if AIDS surrogate testing were not implemented apparently went unheeded?

The questions raised are quite serious. Did blood go untested by over 2 years, despite the availability of tests that could have detected the presence of the AIDS virus or, at the very least, detected those donors at high risk for the disease?

Was the decision not to test made for purely economic reasons, at cost of countless lives and of thousands or perhaps tens of thousands of blood-transfusion recipients now testing positive for the AIDS virus?

Was there a conspiracy of silence by the blood industry and its regulators to hide the problem of transfusion AIDS and to pass the buck to one another in the hope the problem would somehow just go away?

These are just a few of the many, many questions I look forward to having answered as these hearings progress.

Mr. Chairman, I do want to point out that the problems we are today highlighting deal primarily with situations that have occurred in the past. Although I understand our FDA witness will present testimony that problems still exist, it is important for us to recognize the impact that these hearings may have on public confidence in the blood supply. We must seek to get the facts without, at the same time, inducing panic. We in Congress have a great deal of power to influence public opinion, and we must be careful not to abuse that power.

I want to join with you, Mr. Chairman, and with my colleagues in welcoming our witnesses to this hearing. It appears that most of you have been quite courageous in going against the grain and challenging the practices of the blood industry in the areas of testing and donor screening.

I look forward to your testimony and to your ideas on how this subcommittee and its parent committee can work to develop solutions to the extremely troubling questions and problems raised by this investigation.

Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentleman.

The gentleman from Oregon, Mr. Wyden.

Mr. WYDEN. Thank you very much, Mr. Chairman.

I want to commend you, Mr. Chairman, for taking on this issue and, also, for the very responsible way in which I think you have addressed these questions so that the public understands that the blood supply is safer than it has been but, also, that it is important to look at areas where we could do better.

The record shows, in my view, that segments of the blood industry dragged their feet on safety issues in the early 1980's and continue to do so today.

Earlier this week, the public learned that FDA inspectors said the American Red Cross National Headquarters failed to disclose to the FDA 228 instances in which people contracted AIDS or other infections through blood transfusions.

Instead of taking direct responsibility and saying that these reports should have been made to the FDA and will be made in the future, the Red Cross stonewalled the issue and said that such reports were "not required." Now, they are technically correct that they do not have to pass on AIDS cases, but they do have to pass on cases where there are errors, and it seems to me that the position that they have taken, in addition, that the buck should simply be passed on to individual physicians is not the best possible health policy for the future.

The Red Cross, in its statement, also suggested the problems of the early 1980's do not exist today. They believe they are in compliance with their 1988 agreement with the FDA to improve their blood supply operations nationwide, but the subcommittee has documents that indicate that safety problems continue to persist today.

For example, an error report concerning bacterial contamination, where the recipient subsequently died, was discovered in January of 1990 and, as of May of this year, was not reported to the FDA. The report was not even received by the American Red Cross Regulatory Affairs Office until a month after its initial discovery.

So, the notion that these problems are just matters of yesteryear is not one that this member is yet convinced of.

The final point that I would want to mention, Mr. Chairman, is that the slow response of some in the blood industry in the past is undoubtedly going to affect health policy in this country for many years to come. I am concerned that if blood bankers do not move to address the problems outlined by our witnesses today, we may be back looking at some of these continuing problems well into the next century.

Mr. Chairman, again, I commend you for this important inquiry and look forward to working with you.

Mr. DINGELL. The Chair recognizes the gentleman from North Carolina, Mr. McMillan.

Mr. MCMILLAN. Thank you, Mr. Chairman. I commend you for taking urgent action in holding these hearings.

I'll be brief.

We all know that whole blood and its derivatives are absolutely indispensable in modern medicine. It's provided commercially and voluntarily. In my own community, Charlotte, North Carolina, is

dependent upon a major regional Red Cross blood center which, in the past, has had a good reputation. I hope that is the case.

The integrity of supply is absolutely essential. There can be no compromise on that. And the purpose of these hearings today, and those that will follow will be to identify any real problems that have existed in the past, or exist at present; and if so, they're intolerable.

This committee is in a position to recommend immediate action to deal with it if, in fact, the evidence is presented that would indicate that such action is in order.

I appreciate the forthcoming testimony of our witnesses today and look forward to your testimony.

Mr. DINGELL. The Chair thanks the distinguished gentleman.

The Chair recognizes now the gentleman from Georgia, Dr. Rowland.

Mr. ROWLAND. Thank you, Mr. Chairman.

And I commend you for this hearing also.

It's certainly distressing to me to realize that in the early 1980's, when there was increasing evidence that AIDS was spread through transfusion; that for whatever reason, caused a fear of losing donors, the issue was not addressed scientifically.

There were many people, apparently, who were infected that would not have been infected, had the issue been addressed scientifically.

What we need to be concerned with now is the future reliability of the blood supply in our country. I hope we will get information out of this hearing that will focus attention on that and what we need to do in order to ensure that, to the extent possible, we do not have blood that transmits disease from one person to another, in the event of transfusions.

Thank you again, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentleman.

The Chair recognizes now the gentleman from Ohio, Mr. Oxley.

Mr. OXLEY. Thank you, Mr. Chairman.

I don't think I have to remind anyone on this subcommittee, or in this room, that this is a very, very sensitive issue, one that clearly has to be handled in a manner that will not frighten the general public. We must get at the facts; at what has happened in the past and what corrections have been made to change the bad practices of the past.

I know we have a great deal of media interest today. I would simply admonish those in the media that there will be a series of hearings on the blood supply. This is the first hearing, of perhaps four, that this subcommittee will be undertaking. It is critically important it is to place the highest value we can on accuracy, on lack of sensationalism, on trying to get at the facts, and at the same time, give the public the information that they need about our Nation's blood supply.

I know that the Chair is pledged to that effort. The way that this issue has been handled, as usual, has been above any question.

I look forward to hearing from our distinguished panel; and, at a later time, the Red Cross and other agencies that deal with this very difficult problem.

I certainly look forward to participating in those hearings, and I yield back the balance of my time.

Mr. DINGELL. The Chair thanks you.

The gentlewoman from Illinois, Mrs. Collins.

Mrs. COLLINS. Thank you, Mr. Chairman.

Let me add my commendations too, to those who commend you for holding this very timely hearing.

Mr. Chairman, people with severe illnesses come from dozens of other countries in our world, to the United States for treatment because they know that our medical technology and expertise is among the world's best.

Little do they know, however, that there is also a certain percentage of a chance of leaving the United States with more than a cure. In fact, even perhaps with a life threatening disease.

It has come to our attention that our once inviolable blood supply has become susceptible to impurities and contamination. Of course, such instances are far from the norm and there is no need for panic. However, there is a serious need for precautions in order to avoid wide-spread contamination.

If we don't tighten our standards for purity in our blood supply now, we'll be leaving the door open for a spread of disease that could occur in a relatively short time and have far-reaching consequences.

Screening programs ought constantly to be adjusted upward, to reflect the state of the art and understanding of the possible contaminants, as well as the available safeguards against them.

Screening for both HIV-1 and HIV-2, for example, must be as sophisticated as possible and be institutionalized as standard operating procedure, without any kinds of exceptions. If additional testing costs, time and delay are necessary, then so be it. This is simply too serious a matter to cut any corners.

Our committee, as well as Congress as a whole, has devoted a great deal of resources to AIDS-related issues, such as research and development, testing, treatment, confidentiality and various legal ramifications. However, those efforts are futile, without devoting ourselves first and foremost, to prevention.

Unwitting transmission of AIDS-related viruses through blood transfusions and other blood usages, can be absolutely prevented. Our job today is to better understand the problems and the preventive measures that are at our disposal.

Mr. Chairman, I certainly look forward to today's illuminations of the status of our Nation's blood supply; and hopefully, we'll be left with a clear picture, so that we can guard against and be told how to go about doing so.

I again thank you for calling this hearing; and I'm certainly very interested in what our witness is going to say to us, and yield back the balance of our time.

Mr. DINGELL. The Chair thanks the gentlewoman.

The Chair now expresses, first of all, the apology of the Chair to our panel.

We are trying to, at the same time, go to conference with the Senate and to write clean air legislation, in conference with the other body; and for that reason, I was delayed.

I want to also express to all of you, our appreciation here on the committee, for your appearance and for your assistance to us. We are very grateful to you. We view your help as being central to our ability to understand the issues and try and assure that the questions now before the subcommittee are handled in the most responsible and effective and capable manner.

Gentlemen, we will start on your left with Dr. Conant, going across to Mr. Eckert, Dr. Engleman, Mr. Brownstein and Dr. Ratnoff, in that order as we proceed.

Gentlemen, the committee, since its inception, has received all testimony of witnesses under oath.

Do any of you object to appearing under oath?

[Chorus of no's.]

Mr. DINGELL. Gentlemen, the Chair advises also that since that is the practice of the committee, you are—each of you entitled to be advised by counsel during your appearance here.

Do any of you so desire?

[Chorus of no's.]

Mr. DINGELL. Very well. Then for your information, however, to inform you of the powers of the committee—the subcommittee and limitations thereon, as well as your rights, as you appear here before you—copy before us—copies of the rules of the committee, the House and the subcommittee are there before you.

Gentlemen, if you have no objection to appearing under oath, would you each please rise and raise your right hand.

[Witnesses sworn.]

Mr. DINGELL. Gentlemen, please consider yourself under oath.

Dr. Conant, if you would commence, we will recognize you for your statement.

TESTIMONY OF MARCUS A. CONANT, PROFESSOR, UNIVERSITY OF CALIFORNIA MEDICAL CENTER AT SAN FRANCISCO; ROSS D. ECKERT, PROFESSOR, CLAREMONT McKENNA COLLEGE; EDGAR G. ENGLEMAN, MEDICAL DIRECTOR, STANFORD UNIVERSITY BLOOD CENTER; ALAN P. BROWNSTEIN, EXECUTIVE DIRECTOR, NATIONAL HEMOPHILIA FOUNDATION; AND OSCAR D. RATNOFF, HEMATOLOGIST, CASE WESTERN RESERVE UNIVERSITY

Mr. CONANT. Thank you, Mr. Chairman.

Congressman Dingell, distinguished members of the Subcommittee on Oversight and Investigation, ladies and gentlemen, I am Marcus Conant, a Professor at the University of California Medical Center, San Francisco. I co-chair the California State AIDS Leadership Committee and more importantly I care for about 5,000 men and women in San Francisco who are infected with the human immunodeficiency virus that causes AIDS.

I first started seeing patients with AIDS in the Spring of 1981, before the disease was even named AIDS, and have been intimately associated with the epidemic since that time. I started the first multidisciplinary AIDS clinic in the United States at the University of California in 1981. I started the organization that became the San Francisco AIDS Foundation in 1982 and I obtained funds from

the State of California to establish the AIDS Clinical Research Centers at the Universities of California in 1983.

Colleagues and I at the University publicly called on blood bankers to institute surrogate testing of the blood 2 months after the first case of transfusion associated AIDS was reported. Our call to the public was in February of 1983.

The AIDS epidemic as you know was first recognized in Los Angeles, New York and San Francisco in the Spring of 1981 and within a year Dr. Bill Darrow at the CDC had identified that this was a new sexually-transmitted disease. We still didn't know the cause but Dr. Darrow had clearly identified that the disease was being spread by sexual contact.

At about the time of that revelation hemophiliacs were being reported who had contracted this new disease but who had not engaged in homosexual practices. The first three such cases were reported in the MMWR in the Summer of 1982 and speculation began at that time that this new disease might be blood-borne as well as sexually transmitted and might be transmitted in the same way as hepatitis B. That supposition was supported by the report of IV drug users developing AIDS in August and September of 1982. The vertical transmission of AIDS from an infected mother to her child in utero in October of 1982 and finally the first reported case of transfusion associated AIDS in an infant in San Francisco in December of 1982—and that case is illustrative.

The child was born healthy but needed exchange transfusions, about a year later began to suffer from an unusual disease, mycobacterium avium intracellularie, which is a disease seen in AIDS patients, when we started looking for risk factors, we could find none except that the child had had 19 exchange transfusions. When they went back and looked at the donors of those transfusions it was found that one of the men was totally asymptomatic at the time he gave the blood in the Spring of 1981 but was dying of AIDS when the child was found to be sick in the Fall of 1982, telling us that in fact we could have asymptomatic donors who were infectious.

The CDC responded to this information by calling a meeting on January 3rd of 1983 and at that meeting they had members from the blood industry, the hemophiliac industry, the plasma industry. They had representatives from the gay community. Unfortunately they did not have representatives from the general public who would be receiving the blood.

Dr. Spiro pointed out at that meeting that surrogate testing could be used to identify 80 to 95 percent of the patients with AIDS and that surrogate testing could be used to eliminate two-thirds of the people whose behavior had put them at risk for being infected with the AIDS virus.

Blood bankers were reticent to implement these tests and while they agreed at the CDC meeting that something needed to be done, no consensus could be reached as to what should be done.

Two weeks later the blood industry issued a joint statement and made two specific recommendations: (1) that donors be educated as to who was at risk for this new disease so they could self-defer; and that doctors be educated to use less blood in the face of this new

threat. Unfortunately, neither of those recommendations were ever implemented.

In March of 1983 the Public Health Service again reiterated those two requests and suggested that testing be done of donor screening and screening of product to see if the new procedures were working. Again these recommendations were never implemented.

Finally, on March the 24th, 1983 Dr. Petricciani of the Food and Drug Administration issued two sets of regulations, one for whole blood industry and one for the plasma industry with very lenient and vague recommendations for the whole blood industry, slightly more stringent recommendations for the plasma industry even though both are simply arms of the same industry, and while I have no direct evidence for this, it would appear that the recommendations issued by the Food and Drug Administration were the recommendations from the blood industry itself and were not concerned with the evidence of how to stop transfusion associated AIDS to the general public.

Unfortunately these minor steps were the only steps taken during the period of 1983 and 1984 to prevent transfusion associated AIDS and as the number of cases continued to grow, and you will remember that the numbers were being reported on an exponential, innovative techniques to use surrogate screening such as helper/suppressor T-cell ratios which Dr. Engleman was doing at Stanford, hepatitis B core testing which was finally implemented in San Francisco in May of 1984 were not implemented by the national blood industry.

I have suggested the chronology of what occurred until testing became available with an AIDS antibody test in March of 1985 but if I may, let me speculate for a moment as to why this tragedy occurred, a tragedy which has resulted in some 12,000 to 20,000 Americans being infected with the AIDS virus.

The blood bank industry is totally dependent on voluntary free donation of blood by altruistic citizens anxious to help their fellow man. While blood bankers do much good, it is also irrefutable that if donors do not come to blood centers there will be no product to sell to hospitals and patients. Blood bankers were terrified that if they questioned donors about high risk behaviors, donors would cease to present themselves voluntarily to blood centers.

Furthermore, if blood banks did surrogate testing they would have to tell many donors that they had evidence of hepatitis B infection, and this meant the donor was at risk for exposure to the AIDS virus.

Blood bankers feared that both of these steps would threaten the financial viability of the blood banks.

In 1983 blood banking organizations failed us by coordinating their efforts. Their public statement was that the blood was safe, that the chance of getting AIDS from a transfusion was less than a one in a million, and yet the same gentleman who chaired the joint statement committee in January of 1983 at the same time was communicating by memo to his own committee on transfusion transmitted disease and stating that he was certain that there would be more cases of transfusion associated AIDS, that he believed that at this time the most we could do is to buy time, that we were reluc-

tant to do anything publicly for fear that legal authorities would use this information for their own benefit and that we should continue to act together in an effort to control this situation.

This is in February of 1983—so you are having public statements that the blood is safe and private statements from blood bankers that they are certain that there will be more cases and they have to act together to contain the epidemic.

The Centers for Disease Control had identified the cause of AIDS. It had irrefutable evidence of transfusion associated AIDS and yet they were unwilling to use the power of their Agency to move public policy. This could have been achieved by weekly reports of the increasing number of transfusion associated AIDS cases and reports of steps that could be taken to identify individuals at high risk by history and laboratory test.

So the blood industry failed us, the CDC failed us and finally the FDA failed us. The regulatory Agency charged with overseeing the blood banking industry published recommendations that at best were nothing more than watered-down recommendations from the blood banking industry itself and at no time attempted to bring into the review process individuals without ties to the blood bank industry who were expert in evaluation and treatment of patients with AIDS, or representatives from the hospital industry, American medicine or indeed the general public who would be receiving the blood that was drawn from infected donors.

Let me close by telling you why this matter is of such great importance. It is tragic that we have 12,000 to 20,000 Americans infected with AIDS as a consequence of the blood industry drawing donors who could have been deferred, but there is a greater tragedy and the greater tragedy is the fact that the blood industry could have used its tremendous pressure to educate the American people about AIDS, how this disease is transmitted, who is at risk, how to protect yourself and why you should not donate blood if you fall into a high risk group.

Not only did the AIDS epidemic spread by transfusion to individuals because we were drawing from infected donors but because the blood industry failed to go public and to educate the general public, we literally have tens of thousands of young men and women in this country today who could have received information in 1983 and 1984 who were deprived of that information until 1985 and 1986, at which time they became infected—so not only are we going to lose a few thousand people from transfusion associated AIDS, we are going to lose tens of thousands of people because the blood industry did not join with other institutions in educating the American public.

Thank you.

[The prepared statement of Dr. Conant follows:]

STATEMENT OF MARCUS A. CONANT, M.D.

Congressman Dingell, distinguished members of the Subcommittee on Oversight and Investigation, ladies and gentlemen, I am Marcus A. Conant, M.D.; professor at the University of California Medical Center, San Francisco; Co-Chairman of the California AIDS Leadership Committee; and, a physician in private practice caring for 5,000 individuals infected with HIV.

I first started seeing patients with AIDS in the Spring of 1981, and I have been intimately connected with the evaluation and treatment of the disease on a daily

basis since that time. Specifically, I started the first multi-disciplinary AIDS clinic in the United States in the Summer of 1981, I started the organization that became the San Francisco AIDS Foundation in May of 1982, and established the AIDS Clinical Research Center at the University of California Medical Center, San Francisco with funds from the State of California in the Summer of 1983. I was asked to chair the California Task Force on AIDS in 1983 and served as Chairman until I was appointed Co-Chair of the California AIDS Leadership Committee in 1988. My involvement with the disease is accurately chronicled in Randy Shilts' book, "And The Band Played On."

I worked in a blood bank at Duke University for the 4 years I was a medical student, reviewed the procedures of blood banks in 1983, and with colleagues at UCSF issued a warning in 1983 that blood banks needed to do surrogate screening of collected blood to identify those at risk for AIDS and non-A, non-B hepatitis. I personally chaired a California State Task Force in September 1983, and we were assured by the blood industry that they were screening our high risk donors, and that the chance of getting AIDS from a transfusion was less than one in a million.

It is my view that between 12–22,000 Americans were infected with the human immunodeficiency virus (HIV) as a direct result of blood transfusion, because of a failure of blood banks to screen out high risk donors, the failure of the blood industry to accurately disseminate information to their member blood banks, the failure of the regulatory Agency, namely the division of Biologicals of the Food and Drug Administration (FDA), to demand minimum standards of donor evaluation and product screening, and a failure of the Centers for Disease Control (CDC) to demand accountability of the blood industry and the blood regulators.

AIDS was first recognized in Los Angeles, New York and San Francisco in the Spring of 1981. Within a year, Bill Darrow at the Centers for Disease Control, had unquestionably identified this as a new sexually-transmitted disease, which was occurring primarily among (gay) men who were having sex with other men.

Two months later, the first report of AIDS in an individual who was not homosexual, but who had received multiple blood products, some of which could have come from homosexual donors, was reported. This initial report was confirmed by two others, which were reported in the Morbidity and Mortality Weekly Report (MMWR) in July of 1982.

The second clue that this new disease was a sexually-transmitted, blood-borne disease came 2 months later when cases of AIDS among intravenous drug-users were reported from New York and New Jersey. The fact that AIDS was no longer a gay disease was widely reported, and TIME and NEWSWEEK both pointed out that the disease appeared to be spread like Hepatitis B, a sexually-transmitted, blood-borne disease. Soon, women who were the sexual partners of IV-drug users, but who had not used drugs themselves and in whom their drug-using partner were asymptomatic were being reported. This was the first clue that there was a carrier state and that these carriers were infectious. On December the 10th in 1982, Irwin Memorial Blood Bank in San Francisco, in conjunction with Dr. Art Ammann at the University of California, San Francisco and Dr. Selma Dritz, the Chief Epidemiologist for AIDS for the city of San Francisco, reported a child dying of AIDS who had received multiple exchange transfusions. One of the donors was a man who was totally asymptomatic at the time he donated blood in the Spring of 1981, but who dying of AIDS at the time the child was found to be ill. This case clearly pointed to transfusion-associated AIDS.

The Centers for Disease Control immediately responded and called a meeting at the earliest possible date. Because of the upcoming Christmas holidays, that meeting had to be postponed until January the 3rd of 1983. At that meeting, there were representatives from the blood industry, representatives from the hemophiliac community, and representatives from the gay community. Unfortunately absent were representatives from the general public who would be receiving the blood under discussion. Individuals who attended and observed that meeting are in agreement that there was no controversy as to who were the groups at highest risk of infection with AIDS. Dr. Sprio presented overwhelming evidence that surrogate tests, either singularly or in combination, were effective in detecting between 94–98 percent of individuals who had developed AIDS.

The blood industry argued that while there were, at that time, nine hemophiliacs with AIDS who had no other risk factors, and three cases of transfusion-associated AIDS under investigation, that the case for transfusion-associated AIDS had not been definitively proven and that an immediate response was unnecessary. Gay leaders, concerned about the civil rights of their constituents argued that it was inappropriate to question donors about their sexual preference. These leaders favored using surrogate markers such as Hepatitis B core antibody tests and helper/sup-

pressor T-cell ratios to identify individuals who might be at risk for HIV infection. The plasma industry, in response to its market, namely hemophiliac men, argued strongly for deferral of individuals from high risk groups—homosexual men, bisexuals and intravenous drug-users.

While a consensus was reached that something needed to be done, there was no uniform agreement as to what action should be taken.

Two weeks later a joint statement was issued by the blood industry with representatives from the Government and the gay community. This document was ambiguous and had few specific recommendations. The Public Health Service on March 4, 1983 issued specific recommendations that included the need to educate the public as to who should and should not give blood, the need to educate physicians to reduce the amount of blood they were ordering, and the need to test procedures of donor and product screening to be certain that the blood supply was as safe as possible. Unfortunately, these recommendations were never implemented.

Blood banks handed out an important message which is so confusing and ambiguous that it was totally useless as a tool to educate high risk individuals to self-defer. Physicians were not educated to use less blood, but in fact were reassured by the blood industry that the chance of contracting AIDS was less than one in a million. Finally, studies to evaluate donor screening, as recommended by the Public Health Service, were never performed and studies to evaluate laboratory tests to screen blood were poorly designed and poorly executed.

The Food and Drug Administration issued a letter from Dr. Petricciani on March the 24th in 1983 with vague recommendations for blood banks and the plasma industry. It is of interest that while there were three specific recommendations for blood banks, there were six specific recommendations for Plasma collectors. Representatives of the plasma industry wrote to Dr. Petricciani and pointed out the arbitrary distinction he was drawing between blood banks and plasma collectors and asked why he had different standards for the two. While I have no direct evidence to support my hypothesis, it appears that the lenient recommendations of Dr. Petricciani's FDA office for blood banks represent the wishes of the whole-blood industry, while the more stringent recommendations for plasma collectors represent the wishes of the plasma industry and hemophiliac organizations. If true, this suggests that the regulatory Agency of the FDA was responding directly to the industry and not to the concerns of the general public.

The number of transfusion-related AIDS cases continued to rise on an exponential, with the number of reported cases either confirmed or under investigation doubling every 6 months. In spite of the overwhelming evidence that the AIDS virus was present in the blood supply, the blood industry and the Federal regulators did not change their basic position during 1983.

In January of 1984, Curran, et al, published in The New England Journal of Medicine, the final, irrefutable proof that transfusion-associated AIDS was an undeniable reality in American society. They showed that in 7 cases of transfusion-associated AIDS every one of those cases could be traced to a donor from a high risk group. Even with this information, the blood industry continued to downplay the risk of transfusion-associated AIDS, to insist that transfusion-associated AIDS was only possible and had not been proved, and to reassure physicians and patients that everything was being done to screen out high-risk donors.

In fact, nothing was done during 1984 other than the feeble attempts that had been started in 1983. The Federal regulatory Agency did nothing to assure that donor screening policies were evaluated for efficacy or to demand that surrogate testing of blood, which had been implemented at Stanford and in San Francisco, be universally implemented around the country. By the time the HIV antibody test became available in March of 1985, some 15,000 Americans had been infected with HIV. Most of these tragedies could have been avoided with proper donor screening and surrogate testing.

I have recounted the chronology of what occurred, I will now take license to speculate as to why this occurred.

The blood bank industry is totally dependent on voluntary, free donation of blood by altruistic citizens anxious to help their fellow man. While blood bankers do much good, it is also irrefutable that if donors do not come to the blood centers, there will be no product to sell to hospitals and patients. Blood bankers were terrified that if they questioned donors about high risk behavior, donors would cease to present themselves voluntarily at blood banks. Furthermore, if they did surrogate testing, they would have to tell many donors that they had evidence of Hepatitis B infection and that this meant the donor was at risk for exposure to the AIDS virus. Both of these steps could threaten the financial viability of a blood bank.

In 1983, blood banking organizations coordinated their public position that transfusion-associated AIDS had not been proven, but acknowledged privately that they had no doubt that transfusion-associated AIDS was a reality, and that they had to hang together to keep the lawyers away (See Bovie memo).

The Centers for Disease Control had identified the cause of AIDS and had irrefutable evidence of transfusion-associated AIDS and yet they were unwilling to use the power of their Agency to move public policy. This could have been achieved by weekly reports of the increasing number of transfusion-associated AIDS cases and repeated reports of steps that could be taken to identify individuals at high risk both by history and laboratory tests. Finally, the regulatory Agency charged with overseeing the blood banking industry, published recommendations that at best were nothing more than watered-down recommendations from the blood banking industry itself, and at no time attempted to bring into the review process individuals without ties to the blood industry who were expert in the evaluation and treatment of patients with AIDS, or representatives from the hospital industry, American medicine, or the general public who could have been expected to bring a different perspective to the analysis presented by the blood industry.

Let me close by suggesting how the AIDS epidemic, not the just the transfusion-associated epidemic, might look today if the blood industry had done its job in 1983. The exponential rise in the number of AIDS cases in San Francisco occurred between 1980 and 1983. By 1983, the San Francisco AIDS Foundation and other organizations had educated gay men about safe sex, so that when public awareness of the epidemic finally reached a flash point, behavior modification occurred possible, and the percent of individuals seroconverting dropped from 15–20 percent a year to 2–4 percent a year in 12 months. Had blood bankers done what the Public Health Service recommended in March of 1983, they would have gone to the general public, and used the resources of the blood industry to educate the entire American public about the threat of AIDS. Denial centered on the wishful thinking that this was happening only to a small group of homosexual men in New York, Los Angeles and San Francisco could have been swept away. The public would have learned that it was not just gay men with thousands of sexual partners, but anyone with one sexual encounter who could catch this disease. One did not have to be a drug addict, but simply share a needle on one occasion with an infected individual and be at risk for contracting the virus. This information could have been widely disseminated as early as the Spring of 1983 and in my opinion, would have done much to educate the American public about this new threat. Had this been done, not only would we have been spared the majority of the 15,000 Americans who acquired AIDS transfusions, but we would have been spared tens of thousands of deaths of young people in cities across America who only learned that the threat of AIDS was a threat to them as recently as 1987.

Our blood banks failed us, the blood industry failed us, the Centers for Disease Control failed us, and the Food and Drug Administration failed us. And through their failure, many of our patients are now dying from transfusion-associated AIDS and many of our fellow Americans were denied the information about AIDS that would have saved their lives.

Mr. DINGELL. Thank you very much. Dr. Eckert, please proceed.

TESTIMONY OF ROSS D. ECKERT

Mr. ECKERT. Mr. Chairman and members of the subcommittee, thank you very much for inviting me to appear today. My name is Ross D. Eckert. I am Boswell Professor of Economic and Legal Organization at Claremont McKenna College and a member of the Graduate Faculty in Economics of the Claremont Colleges.

I have published two articles and co-authored a book on blood banking and blood safety. I have made several presentations to meetings to the American Association of Blood Banks which are listed on the CV that I submitted to the committee. In 1987, I was appointed by Secretary Bowen to a 4 year term as a member of the FDA's Blood Products Advisory Committee. I appear today in my private capacity as a non-medical expert, and no official support or endorsement by the FDA is intended or should be inferred.

I have written mainly about the non-profit blood banking industry to which I will confine my remarks, and I have submitted a longer statement for the record.

Blood is not as safe today as it can be. We know that some dangerous donors still give and that the tests used by blood banks for HIV and hepatitis viruses have error rates. We have been reminded in the news this week that blood banks also can occasionally make clerical and other errors.

But such errors are probably a small problem compared to the ongoing casualties resulting from inadequate screening of donors throughout blood banking. In 1988, it was estimated that as many as 460 recipients of properly tested blood will be infected with HIV each year. I estimate that for the past several years, about 500 patients a day were infected with hepatitis viruses and that about 4,000 of them per year will develop fatal cirrhosis within 5 to 10 years.

Losing about 4,000 people a year is like losing a fully loaded DC-10 each month. The response of blood banks to the threat of transfusion of AIDS was unnecessarily slow. That slow response had several causes. In most communities, blood banks are monopolies or cartels, so patients lack competitive market processes for protection.

Blood banking, unique among industries, is shielded from strict liability and tort or contract and industry custom is an absolute defense to negligence. Patients are poorly informed about blood safety and rely on the FDA to protect them. Some patients may take fewer precautions in the expectation that the FDA is protecting them.

But the FDA relies heavily on blood banks for advice in setting some of their most important care levels and the three blood collecting organizations often coordinate their policies. Without sufficient competition, liability or regulation, the incentives of blood bankers to provide the service quality that consumers want are relatively weak.

The best way to improve safety is by more careful donor screening. Our donor pool of about 9 million person, each of whom gives only 1.5 times per year on the average, is too large and spreads too much disease. Needed are donor registries, limited panels of low-risk repeat donors who are in good health to begin with, who maintain their health and who are willing to give a more detailed medical history and have their blood tested more carefully than at present.

In 1976, a report to the Congress by the GAO presented evidence that registries in the 1970's at several hospitals improved safety. A test of the experience of a registry using a small selected, targeted and tested donor pool at the Mayo Clinic came to the same conclusion.

Registries in some cities might lead to paying safe donors to donate more frequently. I think we should be willing to buy safe blood if it saves lives, but the blood bankers have opposed even experimenting with registries. The Presidential Commission on the HIV epidemic urged the FDA to fund a 6 month study of registries by an independent organization that would report to the FDA and

the Congress. I urge you to consider that excellent recommendation.

I serve, as I say, on the FDA Blood Products Advisory Committee. From my vantage point on that committee for over 2 years, I have watched the information that the FDA obtains through the Advisory Committee process. That process is heavily skewed in favor of the blood banking industry over consumers.

Individual blood banks and their trade associations regularly appear to present information to the committee and to the Agency. Most consumers are healthy, do not expect to be transfused in a given year, and know next to nothing about blood banking or the FDA's regulatory processes.

Thus, it is not surprising that the FDA gets more information from suppliers than from consumers. The FDA cannot make balanced decisions unless it gets balanced advice. Certain structural changes in the committee would increase the information that the FDA gets from consumers.

First, eliminate the two non-voting positions on the committee. Second, give the consumer representative a vote. Third, appoint physicians in specialties who treat patients having disorders that require heavy use of blood or blood products and who therefore constitute an effective early warning system for the general public.

Fourth, hold the number of voting members who are blood bankers to just one. Fifth, let the committee be chaired by somebody other than a blood banker, and sixth, continue to appoint an economist who can take a society-wide perspective of the change—of the effects of changes in blood safety.

In making these proposals, I emphasize that I am not criticizing any of my individual colleagues on the committee, now or in the past. They are all impressive professionals in the fields that the FDA has selected. In future hearings, I hope that you will learn what it is about the structure of incentives within the FDA that has caused the rate of transfusion casualties from hepatitis and AIDS to be so high and why the surrogate testing matter was handled so terribly.

I hope you will recommend changes in the structure of the Advisory Committee or other measures so that the advice that the FDA receives is fairly balanced. I think those changes are worth making, but I do not believe that they would solve as much of the problem as more competition and product liability would.

I hope you can learn from the blood banking organizations why they issue product statements jointly rather than independently, and why their one in a million statement of the risk of transfusion AIDS in early 1983 was egregiously low. I cannot help but wonder what reprimand the FDA would have issued had a similar exaggeration been made by one of the pharmaceutical firms that it regulates.

Finally, I hope you will explore in future hearings, how the blood bankers and the FDA intend to cope with the next lethal bloodborne virus or other agent when it arrives. Do you they have a

plan, other than to primarily wait for better medical tests to be developed as they did in the case of hepatitis and AIDS? If not, then our society probably faces more rough times ahead. Thank you. I'll be glad to take any questions.

[Testimony resumes on p. 33.]

[The prepared statement of Dr. Eckert follows:]

Statement on the Safety of the Blood Supply by

Ross D. Eckert

before the

Subcommittee on Oversight and Investigations

of the

Committee on Energy and Commerce

U.S. House of Representatives

July 13, 1990

My name is Ross D. Eckert. I am Boswell Professor of Economic and Legal Organization at Claremont McKenna College and member of the Graduate Faculty in Economics of the Claremont Colleges. I have published two articles[1] and coauthored a book[2] on blood banking and blood safety. I have made several presentations to meetings of the American Association of Blood Banks which are listed on the C.V. that I submitted to the subcommittee. In 1987 I was appointed by Secretary Bowen to a four-year term as a member of the FDA's Blood Products Advisory Committee. I appear today in my private capacity as a nonmedical expert; no official support or endorsement by the FDA is intended or should be inferred.

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[1]Eckert, AIDS and the Blood Bankers, REGULATION, Sept./Oct. 1986, at 15-24,54; Quality as a Factor in Competition, in Am. Association of Blood Banks, COMPETITION IN BLOOD SERVICES (G. Clark ed. 1987), at 115-121.

[2]Eckert, Blood, Money and Monopoly, in R. Eckert & E. Wallace, SECURING A SAFER BLOOD SUPPLY: TWO VIEWS (1985), at 1-86.

I have written mainly about the nonprofit blood-banking industry, to which I will confine my remarks.

Blood is Not as Safe as It Can Be

Blood bankers claim that blood now is as safe as it can be, but it isn't. I will explain why it isn't, what the obstacles to safer blood are, and how we can make it safer.

CDC and the Public Health Service have acknowledged that some high-risk individuals still donate. Some donors do not read the information materials they are given; others do not understand them; and some donate even though they know they are in high-risk groups.[3] The test for antibody to HIV is not foolproof owing to the "window period," believed to be up to six months for most persons,[4] during which time an infectious donor may not be detected by the test. In 1988 it was estimated that "as many as 460 recipients of screened blood may become infected annually."[5] The FDA has commissioned a promising study that will attempt

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[3]CDC Study Looks at Why HIV-Seropositive Individuals Donate Blood, COUNCIL OF COMMUNITY BLOOD CENTERS NEWSLETTER, Nov. 10, 1989, at 1-3; Report of the Second Public Health Service AIDS Prevention and Control Conference, 103 PUB. HEALTH REP. 58 (Suppl. 1, 1988).

[4]Hazeltine, Silent HIV Infections, 320 NEW ENG. J. MED. 1487 (1989); Horsburgh, Ou, Jason, et al., Duration of Human Immunodeficiency Virus Infection before Detection of Antibody, LANCET 638 (1989-II).

[5]Ward, Holmberg, Allen, et al., Transmission of Human Immunodeficiency Virus (HIV) by Blood Transfusion Screened as Negative for HIV Antibody, 318 NEW ENG. J. MED. 473 (1988)

to improve donor information materials and to test their effectiveness in blood banks.[6] But how much these improvements can reduce the problem is debatable.

Transfusion AIDS gets the media attention, but transfusion hepatitis is the larger problem. I estimate that from the adoption of surrogate testing in 1987 until the recent introduction of the new test for hepatitis C, probably 5 percent of transfusion patients were infected with hepatitis viruses--over 200,000 persons per year or over 500 per day, 4,000 of whom per year will develop fatal cirrhosis within 5 to 10 years. Losing 4,000 people per year is about like losing a fully-loaded DC-10 each month. I doubt that Congress would tolerate in airline travel the rate of casualties we have had in blood banking.

The blood bankers and the FDA were warned about transfusion AIDS in early 1983. On March 4, 1983 an interagency group of the Public Health Service concluded that "[a]vailable data suggest that . . . AIDS is caused by a transmissible agent" and "[t]he likelihood of blood transmission."[7] In January 1983 CDC fulfilled its duty to warn and recommended either strong donor screening measures

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[6]Mayo, Am. Institutes for Research, DONOR EDUCATION MATERIALS, presentation to FDA Blood Products Advisory Committee, 26th Meeting, Rockville, Md., Sept. 14, 1989.

[7]Centers for Disease Control, U.S. Public Health Service, Prevention of Acquired Immune Deficiency Syndrome (AIDS): Report of Inter-Agency Recommendations, 32 MORBIDITY & MORTALITY WEEKLY REP. No. 8, at 1 (Mar. 4, 1983).

or surrogate testing.[8] Blood bankers and the FDA rejected these prudent recommendations and adopted instead a lamentable series of half-measures.[9] The Presidential Commission on the HIV Epidemic properly concluded that "the initial response of the nation's blood banking industry to the possibility of contamination of the nation's blood by a new infectious agency was unnecessarily slow."[10]

Why did the industry respond so slowly? The reasons are not hard to find. First, blood banks in most communities are monopolies or cartels. Patients who want blood that is safer than what they get "potluck" from their local supplier may have to switch regions as well as physicians and hospitals. For emergencies and many illnesses that is out of the question.

Second, most patients know relatively little about blood safety. They do not understand how blood banks work or what additional precautions they should seek. Usually they do not have time to get information when emergencies or illnesses strike. They rely on hospitals to choose a responsible blood bank, and on the blood bank and the FDA to set correct care levels and to warn physicians about risks.

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[8]Check, Preventing AIDS Transmission: Should Blood Donors Be Screened?, 249 J. A.M.A. 567 (1983).

[9]I have described these inadequacies in AIDS and the Blood Bankers, supra note 1, and in Blood, Money and Monopoly, supra note 2, at ch. 5.

[10]REPORT OF THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC (June 1988), at 78.

Third, minimum standards for screening donors and testing blood are set by the FDA. But for advice on which standards to set, the FDA relies heavily on blood bankers.

Fourth, the penalties consumers can exert against blood banks through the courts are extremely weak. Blood banking, unique among industries, is immune in almost every state from strict liability in tort or contract, usually by "blood shield laws," and industry custom has been an absolute defense against negligence. Industry custom is established primarily by the standards set by the FDA, the American Association of Blood Banks,[11] and the joint policy statements of the three blood-collecting organizations. These organizations used to be rivals. But since January 1983 they have issued at least eight joint statements on screening donors, testing blood, and notifying patients of infected transfusions.[12]

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[11] Am. Association of Blood Banks, Committee on Standards, STANDARDS FOR BLOOD BANKS AND TRANSFUSION SERVICES (P. Holland 13th ed. 1989).

[12] Am. Association of Blood Banks, Am. Red Cross, & Council of Community Blood Centers, JOINT STATEMENT ON ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) RELATED TO TRANSFUSION (Jan. 13, 1983); JOINT STATEMENT ON PREVENTION OF ACQUIRED IMMUNE DEFICIENCY SYNDROME RELATED TO TRANSFUSION (Mar. 7, 1983); JOINT STATEMENT ON DIRECTED DONATIONS AND AIDS (June 22, 1983); JOINT STATEMENT ON LOOK-BACK: NOTIFICATION OF PREVIOUS RECIPIENTS OF BLOOD AND COMPONENTS FROM DONORS WHO NOW HAVE A CONFIRMED POSITIVE TEST FOR ANTI-HTLV-III (June 16, 1986); INTERIM GUIDELINES FOR TESTING DONATED BLOOD FOR HTLV-I ANTIBODIES (Nov. 4, 1988); JOINT STATEMENT ON HIV ANTIGEN TESTING (Apr. 5, 1989); JOINT STATEMENT ON THE INTRODUCTION OF TESTING VOLUNTEER BLOOD DONORS FOR HEPATITIS C VIRUS INFECTION (Apr. 30, 1990); JOINT STATEMENT ON SCREENING BLOOD FOR EVIDENCE OF HIV-2 INFECTION (Apr. 30, 1990).

In sum blood banks are noncompetitive, have as ultimate consumers patients with relatively little information about blood safety, are regulated lightly by the FDA on some of their most important care levels, and are usually free of liability if they follow the minimal industry practices that are heavily influenced by their trade associations. Thus the incentives of blood bankers to provide the service quality that consumers want are relatively weak.

A Solution: Donor Registries

The main reason blood still is unnecessarily dangerous is that our donor pool is too large--over 9 million donors per year, each of whom gives only 1.5 times on the average. An estimated 15 percent are first-time donors,[13] who are relatively risky because they have not been "tested" biologically by previously supplying blood that was transfused without disease.

What we need are registries--limited panels of low-risk repeat donors. Registry donors would be limited to persons who are in good health; who have not been transfused since 1977; who agree to a detailed, confidential medical history, including questions about venereal diseases and sexual promiscuity; and who agree to more extensive testing of blood than is now routine. Registry donors would give only

[13]Sandler, THE CASE FOR ENROLLING AND TESTING, BUT NOT COLLECTING, DURING A DONOR'S FIRST VISIT, presented at the 28th Annual Meeting of the Council of Community Blood Centers, Clearwater, Fla., Feb. 18-22, 1990, at 3.

as often as good health allowed and be replaced only with new, equally well-tested and well-screened donors from the same groups when absolutely necessary.

Many present blood donors would be eligible for registries, but some would not. Many first-time donors would not. Thus the registries that I propose are far more restrictive than what blood banks call registries, which are merely lists of unsatisfactory donors indefinitely deferred.

Better donor screening probably will reduce the amount of laboratory testing needed. Registered donors who meet my proposed criteria probably would not have to be tested at every donation for every test now required. Perhaps some could be done annually. Additional tests may be required initially, but fewer may be necessary over the long run. What would be sufficient would have to be thought through.

Blood banks prefer to use specific laboratory tests rather than donor registries. We know that present donor screening practices are not working well, but blood banks so far have refused to make further adjustments in spite of the available evidence which indicates that registries improve safety. In 1976 a report to the Congress of the General Accounting Office showed that registries in the 1970s at several hospitals were effective.[14] A registry using a "small, selected, targeted and tested donor pool" increased

[14]U.S. General Accounting Office, HEPATITIS FROM BLOOD TRANSFUSIONS: EVALUATION OF METHODS TO REDUCE THE PROBLEM; REPORT TO THE CONGRESS BY THE COMPTROLLER GENERAL 18-23 (Feb. 13, 1976).

safety at the Mayo Clinic in Rochester, Minn.[15] The Mayo Clinic also compared the operating costs of its blood bank during the era when it paid cash versus the period that it did not, and found that noncash donors were more expensive. Noncash donors required more blood bank personnel, more solicitation effort, longer hours of operation, and resulted in harvesting less blood per donor. Unit costs were about half as much with cash donors.[16]

Registries probably would lower costs and increase blood safety. But most blood bankers object on ideological grounds to paying donors cash, which may be necessary in some cities. I would be happy if sufficient quantities of safe blood can be obtained without paying cash. But I have no objection to buying safe blood if it will save lives. If registries reduce transfusion disease in rural Minnesota, then they will probably reduce transfusion disease anywhere.

The Presidential Commission on the HIV Epidemic thought registries deserved further study. It urged the FDA to

> fund an independent scientific organization to initiate a six-month study of the extent, purpose, and effectiveness of existing blood donor registries and the effect that expansion and/or

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[15] Taswell, Directed, Paid and Self Donors, Part III, in COMPETITION IN BLOOD SERVICES, supra note 1, at 147. See also Taswell, director, Mayo Clinic Blood Bank, statement in U.S. Department of Health, Education and Welfare, DEFINITIONS OF VOLUNTARY AND PAID BLOOD DONORS 91a, 93a (Bethesda, Md.: National Institutes of Health Main Campus, 1976); and Kessel, Transfused Blood, Serum Hepatitis, and the Coase Theorem, 17 J. LAW & ECON. 265 (1974).

[16] Taswell, Directed, Paid and Self Donors, Part III, in COMPETITION IN BLOOD SERVICES, supra note 1, at 144-46.

> requirement of donor registries would have on the safety of the blood supply. The independent organization should report the results of such a study to both FDA and the Congress.[17]

The Controversy over Surrogate Testing

In 1973 a study showed that the test for antibody to the hepatitis B core antigen (anti-HBc) was a promising screen for hepatitis.[18] In 1978 a commercial test for anti-HBc was under review for licensing by the FDA.[19] In 1981 two studies showed that testing elevations of a liver enzyme (ALT) could eliminate about a third of hepatitis cases.[20] In 1984 a study showed that the benefits of ALT testing outweighed the costs taking into account replacing donors, and that was before considering lost wages of patients.[21]

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[17] REPORT OF THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC, supra note 10, at 80.

[18] Hoofnagel, Gerety, & Barker, Antibody to Hepatitis-B-Virus Core in Man, LANCET 869 (1973-II);

[19] Hoofnagle, Seeff, Bales, & Zimmerman, Type B Hepatitis after Transfusion with Blood Containing Antibody to Hepatitis Core Antigen, 298 NEW ENG. J. MED. 1379 (1978).

[20] Aach, Szmuness, Moseley, et al., Serum Alanine Aminotransferase of Donors in Relation to the Risk of Non-A, Non-B Hepatitis in Recipients: The Transfusion-Transmitted Viruses Study, 304 NEW ENG. J. MED. 989 (1981); Alter, Purcell, Holland, et al., Donor Transaminase and Recipient Hepatitis: Impact on Blood Transfusion Services, 246 J. A.M.A. 630 (1981).

[21] Silverstein, Mulley, & Dienstag, Should Donor Blood Be Screened for Elevated Alanine Aminotransferase Levels? A Cost-Effectiveness Analysis, 252 J. A.M.A. 2839 (1984).

These publications were all in prominent medical journals. Four blood banks began routine ALT testing in 1982-83.[22]

In March 1983 the Public Health Service announced that the distribution of AIDS cases was parallel to that of hepatitis B virus infection.[23] On July 1, 1983 the Stanford University Blood Bank began to test for reversed T-cell ratios.[24] Blood bankers criticized Stanford for employing a "marketing tool." By March 1984, however, it was clear that Stanford screened some dangerous donors who were allowed to donate at other blood banks.[25]

The blood bankers opposed surrogate testing primarily on the basis of the amount of safe blood it would falsely reject and which they would have to solicit new donors to replace. That is essentially an argument about blood bank operating costs. In February 1986 the FDA Blood Products Advisory Committee recommended using both tests. In 1987, after vacillating for another year, the blood bankers adopted both tests with a lot of grousing about how politics had triumphed over science. But political forces reflected

[22]Remarks of Johanna Pindyck in Am. Association of Blood Banks, LEGAL ISSUES IN TRANSFUSION MEDICINE (G. Clark ed. 1986), at 46-47; telephone conversation with Ronald O. Gilcher, director, Oklahoma Blood Institute, Okla. City, Oct. 18, 1989.

[23]Centers for Disease Control, supra note 7, at 1.

[24]Lifson & Engleman, Second Opinion: Special Report on AIDS, STANFORD MEDICINE, Spring 1985, at 24-25.

[25]Chase, 'Gift of Life' May Be Also an Agent of Death in Some AIDS Cases, Wall St. J., Mar. 12, 1984; Eckert, supra note 2, at 63.

the societal costs of not using surrogate tests much better than the "experts" in blood banks and the FDA did. I would expect that both tests would have been cost-effective for hepatitis before 1982 and for hepatitis and AIDS since 1982. The judgment of the industry and the FDA in delaying the adoption of surrogate testing for so long was miserable. The FDA still does not require either test.

At one time the industry favored abandoning the test for antibody to syphilis. Normal blood bank refrigeration kills the syphilis spirochete, so blood bankers thought the test was an unnecessary expense. Later they recognized that it was a good surrogate marker for sexually promiscuous people who are apt to be at high risk for other transmissible diseases, and who are undesirable donors.

The "One in a Million" Statement

On January 13, 1983 the three blood-collecting organizations said in a joint statement that "[f]ewer than 10 cases of AIDS with possible linkage to transfusion have been seen despite approximately 10 million transfusions per year."[26] The anti-HIV test was implemented in Spring 1985. The test proved to be so effective that it became possible to learn how common HIV infection among blood donors was. The Red Cross surveyed nine of its regional centers and

[26]Am. Association of Blood Banks, Am. Red Cross, & Council of Community Blood Centers, JOINT STATEMENT ON ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) RELATED TO TRANSFUSION (Jan. 13, 1983).

found that the prevalence of true positives was 38 per 100,000, or 380 per million.[27]

The one-in-a-million joint statement was made before the blood bankers could have known what the real risk of transfusion AIDS was, and their estimate was too low by two orders of magnitude. That statement may have led some patients to undergo elective surgeries that they might have postponed if the industry had simply said that it did not know what the risk was. One wonders what type of penalty the FDA would have imposed if a similar exaggeration had been made by one of the pharmaceutical firms it regulates.

The Blood Products Advisory Committee

I have attended eight meetings of the committee beginning in April 1988. During most of 1989 the committee was at full strength with eleven voting members: a hematologist, a pathologist, an economist, five medical school faculty in various specialties, and three blood bankers, one of whom was chairman. The committee also included a nonvoting industry representative and a nonvoting consumer representative.

The committee's "camp followers" consist mainly of blood bankers and the representatives of their three trade associations, manufacturers and the representative of their trade association, journalists, and financial people.

[27] Schorr, Berkowitz, Cumming, et al., Prevalence of HTLV-III Antibody in Blood Donors, 313 NEW ENG. J. MED. 384 (1985).

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Representatives of consumers who are heavy users of blood and blood products appear before us only occasionally. I cannot recall the appearance of any representatives of normally healthy Americans without a history of heavy blood use. That is not surprising. Healthy consumers are not likely to need a transfusion in a given year, and they have little information about blood safety and regulation anyway. Thus the information that the committee and the FDA receive about blood safety is lopsided in favor of suppliers over consumers.

The committee cannot make balanced recommendations, and the FDA cannot make balanced decisions, unless they receive a balance of information. I propose certain structural changes in the committee to strengthen consumers. In making these proposals I emphasize that I am not criticizing any of my individual colleagues on the committee now or in the past; they are impressive professionals in the fields the FDA selected. I also credit the FDA for appointing me--a known critic of blood banking and its regulation. But one appointment is not enough to provide the FDA with the balance of advice that it needs.

First, I recommend that the position of the nonvoting industry representative be eliminated. The committee gets adequate advice from blood products manufacturers from the floor each meeting. Second, the consumer representative should be given a vote. Third, the FDA should appoint still more voting members who are expected to represent consumers.

These would include physicians who specialize in hematology-oncology and who primarily treat patients with diseases that use blood and blood products intensively. Such patients are an important "early warning" system for the community at large, and their interests in safer blood to a great degree match the interests of healthy consumers.

Fourth, it would be sufficient to have just one member who is a blood banker. Blood bankers and their trade association representatives are among the most faithful participants at the committee's meetings, and we get plenty of their advice on almost every subject.

Fifth, a blood banker should not chair the committee.

Sixth, another economist should replace me when my term expires. That person should have interests in health economics and be able to provide a society-wide perspective on the likely effects of changes in blood safety.

Conclusions

I commend the subcommittee for holding this hearing. I hope you pursue your inquiry and make available to the American public more information about the blood banking industry, its regulation, and why things went so wrong.

We need to learn more about the structure of incentives within the FDA that allowed such a high rate of transfusion casualties. Without information about blood banking, market forces, or tort liability to protect them, consumers rely on the FDA. The FDA is supposed to be a consumer-protection

agency, but one would not know it from its regulation of the most important care levels of blood banks. I especially hope that you will discover why the surrogate testing issue was such a fiasco, and that you will recommend changes in the structure of the advisory committee or other measures so that the advice the FDA receives is fairly balanced.

I also hope that you learn why the three blood-collecting organizations issue policy statements jointly rather than independently, and why they made an egregiously low estimate of the risk of transfusion AIDS in 1983.

Finally, I hope you will learn what experts in blood banks and the FDA are doing now to prevent more transfusion casualties when the next lethal blood-borne virus arrives. Do they have a plan? Will they make only minor adjustments in donor screening until new laboratory tests are developed, as they did for AIDS? It took a year to produce the test for antibody to HIV and over twenty years to produce the test for antibody to hepatitis C. Will the blood bankers and the FDA ask our society again to suffer casualties stoically while they wait for specific medical tests? If so, then we face more rough times ahead.

Mr. DINGELL. The committee thanks you. Dr. Engleman.

TESTIMONY OF EDGAR G. ENGLEMAN

Mr. ENGLEMAN. Thank you, Mr. Chairman. My name is Ed Engleman. I am a member of the faculty of the Departments of Pathology and Medicine at Stanford University, and I am also a blood banker and Medical Director of the Stanford University Blood Bank.

In July of 1983, we instituted surrogate testing of our blood donors, in an effort to reduce the transfusion transmission of AIDS. At that time, ours was the first blood bank in the country to institute such testing, although at the time we thought that the need was apparent. And we were quite surprised that the rest of the industry not only did not follow our lead but criticized us for instituting such testing.

We believe that the evidence shows clearly that, had such testing been introduced around the country, and particularly in the high-risk areas, the number of AIDS transfusion cases would have been markedly reduced.

I have provided the committee with a complete transcript of my testimony, and will not take more than the necessary time here. But I do ask that the committee review it in its entirety in the future.

In any event, we believe that the incident of the failure to institute testing for AIDS in 1972 does not represent an isolated problem, since there have been several other problems in failure to institute testing by the blood banking industry, both before and since.

Perhaps a good example is the example of cytomegalovirus, or CMV, for short, for which a simple, inexpensive, and specific test was available as early as 1980. The evidence that the use of this test would prevent transfusion-transmitted CMV disease was published in that year, and yet it took at least 5 years before the industry even acknowledged the potential importance of using this test.

Even today, the use of the CMV test is not mandated for patients who could benefit by CMV-free blood.

In any event, in trying to evaluate the reasons for the failure of the blood banking industry to adopt surrogate testing for AIDS and perhaps for other infectious agents, we have come up with a series of reasons, many of which I think are familiar to you. But they basically boil down to a failure to acknowledge the extent of the AIDS epidemic, an extraordinary resistance to change and criticism, refusal to accept imperfect solutions to urgent problems, and a lack of insightful leadership within the blood banking community and government agencies.

As to what we believe can and should be done now, we are concerned that while the safety of today's blood supply is much improved over past years, that among the reasons for this safety and the reason why we are using so many more tests is public pressure and perhaps fear of litigation on the part of blood banking institutions, rather than insight by the industry into the real needs for the industry.

If this is true, then we have much to fear in the future. I hope that it is not. But one of the ideas that we have recently submitted is the idea that the industry in general and the venerable institutions such as the Red Cross in particular should be subjected to some form of arms-length review at the professional level. Until now, the Red Cross and blood banks in general have reviewed themselves. And it is unfortunate that we don't have a blue ribbon group of professionals that can provide a more objective evaluation than has been carried out in the past.

In addition, we believe that physicians and nurses and health care professionals in general have in the past been extremely poorly trained and educated in the field of transfusion medicine. And we believe that by improving the education of our physicians and nurses, that the consumers and the professionals will be more cautious and more knowledgeable in the future.

I think I will stop there and yield.

[The prepared statement of Dr. Engleman follows:]

STATEMENT OF EDGAR G. ENGLEMAN, M.D., STANFORD UNIVERSITY BLOOD CENTER

My name is Edgar G. Engleman. Since 1978 I have been a member of the faculty of the Stanford University School of Medicine where I am currently professor of Pathology and Medicine, medical Director of the Stanford University Blood Bank, and Associate Medical Director of the Stanford Hospital Transfusion Service, one of the largest in the country. As a physician-scientist, I have carried out basic studies of the human immune system for more than a decade, and for the past 7 years my research laboratory has studied the AIDS virus and its effect on the immune system.

I am here at the invitation of the Subcommittee on Oversight and Investigations to describe the actions taken by our Blood Bank with respect to AIDS in the blood supply, to analyze why the American blood banking system seemed incapable of responding in a timely manner to the AIDS crisis, and to consider what might be done now to maximize transfusion safety. I want to emphasize that it is not my goal to set Stanford apart from or embarrass the blood banking community. Quite the contrary, we at the Stanford Blood Bank are proud to consider ourselves as part of an establishment that has in the main served the public well. Nonetheless, it is our view and the view of the Presidential Commission on AIDS, which studied the problem in detail in 1988, that as a whole the blood banking system reacted too slowly to a major threat to the Nation's blood supply. Our comments are intended to be constructive and to help maximize the safety of the blood supply in the future.

First, in order to understand our own position it is necessary to review Stanford's actions and the response of other blood banks to our actions. On July 1, 1983 (more than 1½ years before a specific test for the AIDS virus was developed—Stanford University Blood Bank became the first in the Nation to screen donated blood with a test designed to reduce transfusion transmission of AIDS. We used specialized reagents and equipment already on hand in our research laboratory to detect a white blood cell abnormality which nearly always occurs in AIDS patients and was also present in many high-risk individuals who felt perfectly well. In contrast to our actions, most other blood banks did not initiate any blood donor screening tests until 1985, and in addition many blood bankers criticized us for initiating our blood donor testing program, arguing that there was no proof that AIDS could be transmitted by blood transfusion and that the test we were using was experimental and too costly.

We felt that AIDS could not be dealt with in the same way as other infectious diseases. Unlike most other infections, AIDS was known to have an extraordinarily long latent phase (that is, the time between exposure and clinical manifestations) and is nearly always fatal. Therefore, while acknowledging that our test (called the T cell ratio test) would probably not detect 100 percent of AIDS carriers and would identify some individuals who were not carriers at all, we nonetheless felt that the benefits of preventing at least some AIDS-contaminated blood from entering the blood supply outweighed the fact that a small amount of normal blood was unavoidably discarded and that each unit of blood cost $6 more. In our view the blood banking community failed to recognize that we could not afford to wait until the causative agent was discovered or until the perfect test was developed. In 1983 and 1984,

we presented our findings to the academic community, to blood bankers, and to the FDA, and repeatedly spoke out in public on the need to implement available screening tests, imperfect though they might be, to reduce the risk of transmitting AIDS by transfusion. In an attempt to publicly bring the matter out for discussion in the blood banking community, in the summer of 1983 we submitted an abstract on the subject for presentation to the annual national meeting of the American Association of Blood Banks (AABB). In that abstract, we cited the need for blood testing to reduce the risk of transmitting AIDS by transfusion, described how the T cell test was performed, and reported on its use in our blood bank. Although we were disappointed that our abstract was rejected for presentation at that meeting, it was particularly distressing to discover later that the subject of transfusion-associated AIDS wasn't even on the meeting's program. While we certainly don't believe that there was a conscious conspiracy to repress information about transfusion-associated AIDS, there seemed to be great reluctance among blood bankers to acknowledge the problem.

The efficacy of our screening program and the need for some form of laboratory testing to supplement voluntary self-deferral of high-risk donors were demonstrated in the summer of 1983. Follow-up interviews revealed that several donors whose blood was excluded from transfusion on the basis of our screening test had, in fact, donated despite belonging to AIDS high-risk groups. The point was further underscored in early 1984 when we learned that a donor whose blood our test rejected had been hospitalized with AIDS some 8 months after his attempted blood donation. Subsequent to the introduction of the specific AIDS virus (HIV) antibody test in 1985, we retrospectively tested frozen blood from donors whose T cell tests had been abnormal, and found that the T cell test had successfully identified approximately two-thirds of the HIV infected individuals who had donated blood—not a perfect result, but significantly better than doing no testing at all.

Before leaving the subject of these early, indirect tests for AIDS, it is important to emphasize that while we chose to use a test that would have been difficult for many blood banks to adopt quickly, other more feasible tests were also available and used by some blood banks, but rejected by the vast majority. The most prominent example was the test for antibody to the core component of hepatitis B. This was a relatively inexpensive test which utilized equipment already on hand at most blood banks. While this test, like the T cell test, was far from perfect, retrospective analysis has shown conclusively that had the test been used on blood donors, it would have markedly reduced the rate of HIV transmission via transfusion without seriously jeopardizing the blood supply.

Why did the blood banking leadership, national organizations such as the AABB and Red Cross, as well as Government agencies such as the FDA, fail to recommend any additional testing of donor blood prior to the introduction of the HIV antibody test in 1985? We believe that there were several contributing factors, but they basically boiled down to a failure to acknowledge the extent of the AIDS epidemic, an extraordinary resistance to change and criticism, a refusal to accept imperfect solutions to urgent problems, and a lack of insightful leadership within the blood banking community and government agencies. Allow me to cite a few examples which support this analysis. One example antedates the AIDS epidemic altogether. In 1980, my colleagues at Stanford, Drs. Ann Yeager and Carl Grumet, developed a simple blood test for the presence of antibodies to cytomegalovirus (CMV), applied this test to donated blood and demonstrated that by using only CMV seronegative blood, the devastating clinical consequences of transfusion-transmitted CMV infection in premature infants could be completely avoided. The cost of the test was no more than $2 and the results, which were published in peer-reviewed medical journals, were clear-cut (e.g., see A.S. Yeager, F.C. Grumet, et al. Prevention of transfusion-acquired cytomegalovirus infections in newborn infants. Journal of Pediatrics, volume 98, pages 281–87, 1981). Yet for 5 years after the results were published, the AABB and the Red Cross did not endorse CMV testing, and many blood bankers called such testing impractical or inexact, a theme we heard again when the early indirect AIDS screening tests were introduced. Note that in contrast to the AIDS epidemic, where we were forced to rely on indirect tests until 1985, when it came to CMV we had an inexpensive and highly specific test. Moreover, there was hard evidence that by using the test in well-defined clinical situations, substantial morbidity and mortality could be avoided. Thus, it should come as no surprise that indirect blood tests for AIDS were rejected. In our view, until recently the industry as well as the FDA have steadfastly resisted the addition of new tests, requiring that the utility of any candidate test be proven over and over and over again before it can even be considered for recommended use.

In 1983, concern about the possibility that the blood supply was contaminated with the AIDS agent began to alarm the public. However, even as the public lost confidence in the safety of the blood supply, blood banking organizations failed to understand the public's concern and did not respond appropriately. Thus, for example, as increasing numbers of anxious patients began to request directed donations (that is, the specified use of a particular donor's blood for a particular patient), most blood banks simply denied the requests, and blood banking organizations issued press releases condemning the practice of directed donations. While there is no guarantee that one's relatives and friends are either safer or less safe blood donors, and the maintenance of a separate inventory of blood products for individual patients presents a costly administrative burden, in our view the recalcitrance of blood banks served only to intensify the public's concerns and, ultimately, helped to spawn the appearance of costly, for-profit "boutique" blood banks.

Another problem relates to the failure of blood banks to aggressively recommend and make available autologous blood (that is, one's own blood, which often can be donated during the month prior to an elective surgical procedure for subsequent use during or immediately after that procedure) to patients. There is no question that one's own blood constitutes by far the safest blood, since it does not expose patients to any infectious agents to which they are not already exposed. While most blood banks did not refuse to provide autologous blood, they did not necessarily encourage its use and may have inadvertently discouraged it by, for example, limiting the locations and hours available for autologous donations. Unfortunately, over the past few years community blood banks have become inundated as they attempt to incorporate new, mandated blood tests and look back programs associated with the AIDS epidemic, while struggling with enormous pressures to contain costs. As a result, autologous and patient-directed donor programs represent additional burdens on already overburdened facilities and staffs.

What, if anything, should be done now to assure a safer blood supply? An argument could be made that the AIDS tragedy appears to have already led to significant improvements in the responsiveness of blood banking organizations. For example, blood tests similar to those rejected by blood bankers for the prevention of AIDS in 1983 to 1985, are now used by virtually all blood banks to minimize transmission of non-A, non-B hepatitis, an infectious disorder which occurred in as many as 5–10 percent of all transfusion recipients prior to the institution of these tests. Similarly, tests for the HTLV-I leukemia virus and for the newly identified hepatitis C virus, have recently been universally instituted. Were it not for the impact of the AIDS epidemic and the public reaction to the failure of blood banks to take aggressive preventative actions, we seriously doubt that most of these new tests would be in place today. The same pressures on blood banks are probably responsible for the general availability of donor directed and autologous blood transfusion programs. Although it is regrettable that it took an AIDS epidemic to break down the barriers of complacency and resistance to change in the blood banking industry, the benefits of these new programs are real and likely, in our view, to be long-lasting.

Does this mean that all is now well and that the future safety of the blood supply is assured? Unfortunately, there is reason for continued concern. First, we are distressed that so many blood bankers and organizations still do not understand that more could have been done from 1983 to 1985 to prevent transfusion-associated AIDS. This suggests that they simply do not realize that the system failed or that it has flaws. If so, then the recent adoption of stringent new blood testing procedures may possibly represent a response to public pressure or fear of litigation rather than a result of self-examination. When the current public outcry abates can we be confident that the industry will respond any differently to future, unforeseen problems? Considering the enormous consequences of decisions made by blood banks in 1983 and 1984, a formal inquiry into the industry's performance seems to us long overdue, and hopefully the current hearings will serve this purpose.

While we do not want to prejudge the conclusions of this committee, we would like to take this opportunity to suggest a number of specific steps which we hope would be seriously considered. First, there should be increased emphasis on transfusion medicine in the education of our health care professionals. In the past there has been little emphasis on transfusion medicine principles and options in the education of physicians and nurses. As a result, many physicians and nurses are relatively poorly trained with respect to the indications for transfusion, and they are even less knowledgeable about the potential complications. Blood is a life-saving but nonetheless potentially dangerous agent which should be treated no differently than other dangerous intravenous medicines, and there is no excuse for our professional schools not to better educate future health care professionals on the proper use of transfusions.

Second, we believe that government sponsorship of biomedical research on the problems associated with transfusion should be encouraged in the form of targeted contracts and grants. The National Heart, Lung and Blood Institute (of the National Institutes of health) went on record several years ago as recognizing the need to support educational and research endeavors in the field of transfusion medicine. To its credit the Institute funded several Specialized Centers of Research in Transfusion Medicine and has provided some limited funding for education in transfusion medicine. These efforts should be applauded but viewed as only the beginning. Additional support for education and innovation in transfusion medicine is urgently needed.

Finally, we must take steps to insure that the innovators are heard and discoveries applied quickly by the blood banking community. In order to facilitate a more rapid response to future problems and to translate basic research findings into practical ends, closer relationships between blood banks and medical research and teaching institutions should be fostered. We must not lose sight of the fact that the practice of blood banking is a practice of medicine. Unfortunately, increasing emphasis on cost containment and efficiency has tended to encourage excessive centralization while discouraging innovation, and all too often has led to the subordination of medical direction to lay management. Perhaps this contributed to the hesitance of blood banks to meet the AIDS challenge more aggressively, and perhaps this is responsible, in part, for the relatively small investment in research made by the major blood banking organization.

The contributions of the American Red Cross and the American Association of Blood Banks have been substantial and should be recognized. However, these venerable institutions must not be impervious to constructive criticism lest they risk losing their effectiveness as well as the public's confidence. Only through a concerted effort aimed at evaluating the industry's performance, educating health care personnel on the principles of transfusion medicine, and supporting innovative research can we expect to be ready for future challenges.

Mr. DINGELL. We thank you very much. Dr. Brownstein.

TESTIMONY OF ALAN P. BROWNSTEIN

Mr. BROWNSTEIN. Thank you, Mr. Chairman and members of the subcommittee. My name is Alan Brownstein and I am the Executive Director of The National Hemophilia Foundation. I have held that position since 1981 and have seen a tremendous tragedy occur to the many individuals with hemophilia because of the contamination of the blood supply by the AIDS virus.

Mr. Chairman, we deeply appreciate the opportunity to testify on these important issues and to share our experience with you. NHF believes that the safety of the Nation's blood supply is measured by the health and well-being of the people who use it. Our confidence in that safety was shaken greatly in the 1980's. We hope that the result of your investigation will be a renewed faith in the safety of blood for everyone.

Hemophilia is an inherited defect of the blood clotting mechanism that affects 20,000, almost all males. Deficiencies in Factor VIII (hemophilia A) and Factor IX (hemophilia B) are the most prevalent and a deficiency in either can cause severe bleeding problems. An individual with severe hemophilia may bleed spontaneously without trauma 30–50 times a year. Each person with severe hemophilia A uses an average of 50,000–80,000 units of clotting factor each year. Because this clotting factor is produced from the blood plasma of many donors, well over 100,000 donors per year, these individuals are exposed to many transfusion borne risks. For example, hepatitis is also a major risk for the individual with hemophilia.

In July of 1982, CDC reported three cases of AIDS among hemophilia patients. It is now estimated that 50 percent of all persons

with hemophilia are HIV positive. Seropositivity rates for persons with sever hemophilia are about 70 percent. The total number of patients diagnosed with AIDS according to CDC as of May of 1990, is now 1,424. Of these, 950 have already died. Children are also vulnerable as 119 of these cases are under the age of 13.

The impact of this disease on people with hemophilia, their families and loved ones has been enormous. While we are optimistic about the potential of new drugs to treat AIDS, nonetheless, half of our population is HIV positive and faces an uncertain future. In addition to the loss of life caused by AIDS among people with hemophilia, there are other consequences. As we have seen from the tragic events surrounding the life of Ryan White, people with hemophilia have been subject to discrimination at school or at work.

Another result has been the enormous increase in the cost of treating hemophilia. New clotting factors which are viral inactivated to protect against HIV cost substantially more than previous products. In just a year and a half, price increases of 600–800 percent were typical. Since July of 1982, when I was first informed by Dr. Bruce Evatt of CDC that three people with hemophilia had been diagnosed with AIDS, NHF has been aggressive in its efforts to assure a safe blood supply to get effective treatments that are free of viruses and to provide assistance to our community.

We immediately alerted our chapters and health professionals about the presence of AIDS. By October of 1982, even though definitive data linking AIDS to the blood supply was lacking, we felt that steps needed to be taken to protect the blood supply until it could be established that it was free of the HIV virus. We recommended that vigorous steps be taken to exclude donors who were known to be at high risk of contracting AIDS. We distributed this position widely in November of 1982; however, we were deeply disappointed that no public policy emerged at that time.

Mr. Chairman, NHF was incensed that there was a lack of willingness to officially acknowledge the potential seriousness of this situation. We urged the Public Health Service to address this problem as soon as possible. Unfortunately, their meeting on January 4, 1983, did not lead to any new policies. In fact, the number of blood bank executives who attended that meeting objected to any course of action unless definitive scientific information was provided. Then the NHF convened an emergency meeting of its prestigious Medical and Scientific Advisory Council on January 14, 1983, to develop a position of AIDS in relation to blood product safety.

MASAC, as we call it, reviewed the data that had been reported at the January 4th meeting and recommended that it was important to screen and exclude high risk donors from the blood and plasma supply used in the production of material prepared for the treatment of hemophilia. We also called for evaluation and implementation of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission. Our recommendations were immediately accepted by the blood fractionation industry but not the blood banking community with respect to donor screening.

Within 2 months, however, the Public Health Service issued recommendations embodying the concepts endorsed by our MASAC, and shortly thereafter the voluntary blood banks followed suit. Thus, NHF was the first national body to spearhead a broad based

awareness of the need for safeguarding the Nation's blood supply, because in a very real way we served as an early warning system to the general public due to our vast exposure to blood and blood products.

Since then, we have issued policies that were followed by the industry that lead to numerous product withdrawals, screening donors for HIV related symptoms, and ALT testing. By mid-August, we will be issuing recommendations regarding hepatitis C testing and we will also be examining HIV, too.

What can be done to make sure that the blood supply is not similarly affected in the future? Based on the experience we have over the last several years, we have several recommendations to make in closing.

First, it is important to strengthen the FDA's regulatory role over new technology blood products. We believe you must give FDA authority to monitor products once they have been approved for sale so that the long term effects can be assessed. Additionally, FDA must have the resources, both financially and human, to fulfill its mandates. Only then will it be able to speed the review and approval of new, non-human source blood products as well as new viral inactivation methods.

Second, the Nation needs to devote greater resources to assuring safety in the collection of our blood supply. This means that CDC needs to conduct more epidemiologic studies that will lead to the development of more effective donor screening criteria. Also, FDA needs to expedite the review and assessment of improved methods of testing blood.

And finally, we need to take steps to address the cost issues that have arisen for hemophilia treatment. Not only must the reimbursement system recognize the changing technologies when they occur, we also need to protect individuals with chronic conditions, such as hemophilia, from discrimination in the insurance market.

Mr. Chairman, again I want to express my thanks to you and the members of the subcommittee for holding these important hearings and conducting this investigation. A great tragedy has occurred with the contamination of the blood supply by the HIV virus. This must not happen again. We urge Congress to take the steps necessary to ensure that we never have a repeat of this tragic circumstance. The National Hemophilia Foundation pledges its full resources to work with you.

I would pleased to answer any questions from any members of this subcommittee. I thank you.

[Testimony resumes on p. 62.]

[The prepared statement and attachments of Dr. Brownstein follow:]

STATEMENT OF THE NATIONAL HEMOPHILIA FOUNDATION
TO THE
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE

Presented by

Alan P. Brownstein, MPH, MSW
Executive Director

Mr. Chairman and Members of the Subcommittee:

My name is Alan P. Brownstein, MPH, MSW, and I am the Executive Director of the National Hemophilia Foundation (NHF). I have been Executive Director since 1981 and, in that time, have seen a tremendous tragedy occur to many individuals with hemophilia because of the contamination of the blood supply by the AIDS virus. NHF is a nonprofit, consumer advocate association representing the approximately 20,000 people in the United States with hemophilia. We provide an array of information, programs and assistance to these individuals, their families and the health professionals who treat them.

I would like to present to the Subcommittee information on hemophilia as a genetic bleeding disorder, the impact of HIV infection on individuals with hemophilia, the response of NHF to this situation, and finally, our recommendations on how to prevent similar tragedies. The attached articles from the Journal of the American Medical Association contains additional information.

Mr. Chairman, we deeply appreciate this opportunity to testify on these important issues and to share our experience with you. NHF believes that the safety of the nation's blood supply is measured by the health and well being of the people who use it. Regrettably our confidence has been greatly shaken. Because of our dependence on the blood supply, people with hemophilia serve as an early warning signal when problems occur.

BACKGROUND ON HEMOPHILIA

Hemophilia is an inherited defect of the blood clotting mechanism. There are many known blood clotting factors. Deficiencies in Factors VIII (hemophilia A) and IX (hemophilia B) are the most prevalent and a deficiency in either of these can cause severe bleeding problems. Persons with hemophilia are almost always male and suffer the effects of this condition for their lifetimes.

Individuals with hemophilia are characterized as having severe, moderate, or mild disease. An individual with severe disease may bleed spontaneously without trauma 30-50 times a year. Patients who are categorized as moderate, bleed with mild trauma. Mild patients will bleed only with severe trauma. Of the NHF estimated population of 20,000 people with hemophilia, approximately 17,000 persons have hemophilia A and, of that number, 60% to 70% are classified as severe. Each person with severe hemophilia A uses on average 50,000 to 80,000 units of clotting factor each year. Mild or moderate persons with hemophilia can use anywhere from 0-20,000 units annually. The annual use in the United State of factor VIII to treat hemophilia A is approximately 500-550 million units. An additional 75 million units of Factor IX are used for individuals with Factor IX deficiency, and another 75 million units of Factor IX are used for patients who have developed inhibitors to Factor VIII.

For the individual with severe hemophilia, internal hemorrhaging can begin with no apparent cause. Unless this hemorrhaging is stopped, blood can seep into joints and soft tissues. Such hemorrhages can result in joint deformity and limited mobility. Uncontrolled bleeding can also lead to death. Since the individual with hemophilia cannot rely on the normal clotting process to stop the loss of blood, he must replace the missing factor VIII or IX with commercially prepared concentrates. These concentrates are currently derived from blood plasma collected from paid and volunteer donors.

Individuals with hemophilia will be almost totally reliant on human blood as a basis for their treatment until a cure is found or a clotting factor is developed that is not based on human blood. Thus, the safety of the nation's blood supply is critical to us. Any breakdown, as occurred with the AIDS virus, can be devastating.

While my discussion today will focus on AIDS, many other blood borne viruses and contaminants can have a debilitating or deadly affect on persons with hemophilia. Hepatitis, for example, continues to be a major risk for the individual with hemophilia. Again, let me emphasize the fact that as long as the treatment of hemophilia relies on human blood products, individuals will be exposed to some transfusion borne risk.

It is the great irony of hemophilia that the development of

clotting factor allowed a liberation of the individual with hemophilia from this chronic condition. Yet it is the contamination of these clotting factors with HIV virus that has brought us to this table today.

We would like to sketch for the Subcommittee a brief history of clotting factor and the treatment of hemophilia. Prior to 1950, bleeding episodes were often treated by infusions of whole blood. After 1950, fresh frozen plasma was used. During the 1960s, a number of scientific discoveries permitted a greater understanding of the nature of hemophilia and the ways in which it might be managed. The use of cryoprecipitate was initiated. Each of these treatments, while important steps forward, had its drawbacks. NHF urged industry to devise new methods of treatment.

In the 1970s, a new technology, clotting factor concentrates, became widely available and methods were devised to improve the delivery of treatment to individuals with hemophilia. Many advances in comprehensive care were initiated. Home infusion became a reality, meaning that the individual with hemophilia no longer had to go to the hospital for each bleeding episode. A particularly important event for hemophilia was the development by Congress of a system of comprehensive hemophilia treatment centers, funded through the Maternal and Child Health grant program. This network of centers not only helped advance the treatment of hemophilia, it was also available to our community when AIDS began

to exact its terrible toll. The presence of an organized health care system for hemophilia has been a tremendous boon to families, individuals with hemophilia and health professionals who treat them as the AIDS crisis has progressed.

In the 1980s, further refinements were made in the treatment of clotting factor. After the discovery of the HIV contamination of the blood supply, new methods were developed to inactivate viruses. These have lead to clotting factor that is HIV virally inactive. These methods may also have the potential to inactivate other viruses.

Prior to the contamination of clotting factor it had been the release from disability for many people with hemophilia. Thanks to Congressional support, advances in treatment and the success of the comprehensive care system had led to dramatic changes in the lives of persons with hemophilia and in the costs associated in treating this disease. An evaluation of 31 federally funded treatment centers showed remarkable findings over the period 1975-1985, including the following:

- the number of patients in home care increased by 326 percent;

- the average days per year lost from work or school declined by 73 percent;

- the average hospital admissions annually declined 88 percent;
- the average days per year spent as an inpatient declined 83 percent;
- patients' out of pocket spending declined 77 percent;
- the overall annual cost of caring for the patient with hemophilia declined by 74 percent; and
- unemployment declined 74 percent.

These changes are dramatic and demonstrate what has been accomplished through a combination of good research, quality medical care and strong social support systems as provided through the comprehensive treatment centers.

AIDS AND HEMOPHILIA

In July 1982, the Centers for Disease Control (CDC) reported three cases of AIDS identified among hemophilia patients. It is now estimated that 50% of all persons with hemophilia are HIV seropositive. Seropositivity rates for persons with severe hemophilia range from 70-80%.

These astounding figures result from the procedures used to

manufacture concentrate. Plasma is collected from many donors and pooled. This results in a person with hemophilia being potentially exposed to anywhere from 4,000-48,000 donors at any one time. Since severe hemophilia patients can treat bleeding episodes as many as 30-50 times annually, they can be exposed to hundreds of thousands of donors. The opportunity for infection is immense. This was true of HIV and would be true of any other blood borne disease.

The total number of individuals diagnosed with AIDS according to the CDC HIV/AIDS surveillance report (January 1990) was 1318. Of these, 837 have died. Children are especially vulnerable and 109 under 13 years of age have AIDS. Many have died.

The impact of this disease on individuals with hemophilia, their families and loved ones has been enormous. While we are optimistic about the potential of new drugs to treat AIDS, nonetheless, half of our population is HIV positive and faces an uncertain future.

In addition to the loss of life caused by AIDS among people with hemophilia, there have been other consequences with enormous impact on individuals and their families which have been the direct result of HIV contamination of the blood supply. One of these has been the discrimination experienced by individuals with hemophilia who have become HIV positive or developed AIDS. We need only look at recent events surrounding the life of Ryan White, a young man with

hemophilia who tragically died of AIDS, to see the terrible impact that fear, hysteria and discrimination have had on our community. Not all discrimination has been so blatant. Often it is subtle, but the effects are just as real. Individuals with hemophilia who had made great progress in reducing their dependency are now finding that they must "go into hiding" because of fear of discrimination at school or in the work place.

Another result has been an enormous increase in the cost burdens of this disease. The price of clotting factor, virally inactivated to protect the person with hemophilia against HIV, has increased at a dramatic rate. Price increases of 600-800 percent are not unknown. While we recognize and are encouraged by the efforts of the manufacturers to develop new products, and we appreciate the cost they had to bear in order to do this, there is no question that these increased costs are a double tragedy for individuals with hemophilia and their families. Parents of a child with hemophilia realize that the lifetime limits of their health insurance will be exhausted well before their child reaches maturity. The resources of the hemophilia treatment centers are increasingly strapped to deal with these costs. State treatment programs are also hard pressed to find money to meet these costs. Individuals with hemophilia are reluctant to change jobs for fear that preexisting condition limitations in health insurance policies will preclude coverage of clotting factor. Since few families can absorb as much as $100,000 annually in uninsured health care costs,

changes in employment become increasingly difficult to make. This increased expense comes at a time when health insurance companies and employers are increasingly looking to reduce their expenditures. Coverage limitations are becoming more common. Thus, even for the individual who has health insurance, the difficulty of managing these kinds of expenses is increased.

NHF'S RESPONSE TO THE AIDS CRISIS

What has been the role of the National Hemophilia Foundation through the years as this crisis developed? Since the earliest days, NHF has vigorously called attention to the need to protect the blood supply, through governmental and private action. We have urged the development of safer blood products and we have shared our best knowledge with health professionals, people with hemophilia and their families.

Our first medical bulletin on HIV was sent out in July 1982, immediately after the Centers for Disease Control (CDC) identified HIV in three persons with hemophilia. NHF quickly become involved with the Department of Health and Human Services in its overall efforts to deal with the disease. Then NHF President, Charles J. Carmen, and medical co-director, Louis Aledort, M.D., attended a meeting in Washington, D.C., on July 27, 1982, as members of a special panel convened by the Department of Health and Human Services to review the significance of these findings to

hemophilia.

On December 21, 1982 we issued our first advisory on the implication of HIV/AIDS regarding blood product use. We recommended that "this is no time to introduce concentrate to patients who have never used them before, except when there is an overriding medical indication." On January 14, 1983, our Medical and Scientific Advisory Council (MASAC) made a series of recommendations to treaters on ways to prevent AIDS in patients with hemophilia. In that same bulletin, recommendations were made to factor VIII manufacturers, including a call for serious efforts to exclude donors who could transmit AIDS. Additionally, we called for industry efforts to expedite the development of processing methods that would inactivate viruses potentially present in Factor VIII concentrate. We urged FDA to approve quickly these new, virally safe products. These efforts continue today.

We petitioned Congress for more resources for AIDS treatment and research. We have sought new laws to end discrimination. We have worked to expand Medicare and private reimbursement for costly new products. We continue to issue regular bulletins on developments in AIDS research, treatment and education.

RECOMMENDATIONS

As the National Hemophilia Foundation has worked through the crisis

caused by the HIV contamination of the blood supply and its resulting impacts on individuals with hemophilia, we have learned much. Based on our experience, we make the following recommendations to the Subcommittee and Congress that could prevent future tragedies of this type.

First, FDA's regulatory role over blood products is crucial to us and it must be strengthened. We ask you to give FDA the fullest power to protect the safety of the blood supply and blood products. We also believe that FDA's authority to monitor products once they have been approved for sale should be expanded. Adverse reactions need to be reported so that appropriate follow up can be instituted. This must be a cooperative effort between the FDA, the industry, treaters and consumers of these products. FDA must have the resources, both financial and human, to fulfill its mandate. This includes speeding review and approval of new viral testing methods, new non-human source blood products and new viral inactivation methods.

Second, the nation needs to devote greater resources, both public and private, to assuring the safety of our blood supply. Not only is it critical to individuals with hemophilia, it is essential to all persons who might come in contact with blood products. We need a greater understanding of the factors that can affect blood safety and how to deal with them. CDC needs to conduct epidemiological studies that will lead to the development of more effective donor

exclusion criteria.

Third, steps must be taken to address the cost issues of treating hemophilia. Importantly, this means some modification to health insurance which is the system through which most individuals with hemophilia receive their medical care coverage. The existence of restrictions on preexisting conditions as well as other forms of limitations that serve to discriminate against the individual with hemophilia must be identified and stopped. NHF supports legislation which would restrict the ability of insurance companies to use the preexisting condition as an underwriting tool. If we are to depend on a mix of public and private insurance to provide health care coverage for Americans, then we cannot permit the a part of that system to discriminate. Government payment programs must also share in solving this problem. Medicare and Medicaid must continue to be responsive to the needs of beneficiaries with hemophilia and recognize new treatments when they become available.

Mr. Chairman, this concludes my statement. We appreciate the interest and concern of the Subcommittee. I would be pleased to answer any questions the Members of the Subcommittee may have.

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THE TREATMENT OF HEMOPHILIA

Past Tragedy and Future Promise

Concentrated preparations of factor VIII became commercially available in 1965 and were soon widely used in the United States and throughout the world to treat hemophilia. The development of these concentrates represented a tremendous therapeutic advance. The enthusiasm that greeted them was only mildly dampened by the early realization that all factor VIII products were contaminated with hepatitis viruses and by the resulting epidemic of hepatitis B and non-A, non-B hepatitis among people with hemophilia. Although 90 percent of the patients severely affected with hemophilia eventually became seropositive for hepatitis B antibody and although non-A, non-B hepatitis was thought to develop in virtually 100 percent, the consequences of chronic liver disease were considered to be acceptable, given the alternative risk of hemorrhagic complications. Nevertheless, attempts by the manufacturers of factor VIII products to inactivate hepatitis viruses and other viral contaminants were welcomed. At about the same time, the acquired immunodeficiency syndrome (AIDS) began to receive increasing attention, especially the possibility that it was due to a virus that could be transmitted by blood and blood products. From the retrospective analysis of stored serum samples, we now know that human immunodeficiency virus (HIV) seroconversion occurred in some patients with hemophilia as early as 1978.

The prospective study of HIV type 1 infection and AIDS in patients with hemophilia reported in this issue of the *Journal* illustrates the tragic consequences of the contamination of factor VIII products with HIV.[1] In the United States, where factor VIII products that were not heat-treated were used extensively for replacement therapy, the incidence of HIV positivity ranges from about 50 to 90 percent in severely affected patients. The article by Goedert and colleagues clearly indicates that unless an effective ther-

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apy for HIV infection is found, the infection will inexorably progress to clinical AIDS in an increasing number of HIV-positive patients with hemophilia.[1] Although this study adds valuable prognostic information about the development of AIDS, those of us who treat patients with hemophilia can take little comfort in the knowledge that the cumulative rate of AIDS is lower in younger than in older groups, or that certain markers such as low levels of CD4 lymphocytes and the loss of anti-p24 antibodies are predictors of the early development of AIDS. Although this knowledge may eventually lead to improved therapy, it is unlikely that this will happen within the anticipated life span of currently infected patients.

Despite the despair that people with hemophilia and their physicians now feel, the future for those who are not yet infected with HIV is now much brighter, as the article by Schimpf et al.[2] in this issue of the *Journal* indicates. These investigators have clearly shown that pasteurized factor VIII concentrates, even those prepared from unscreened plasma, do not contain infectious HIV-1 or HIV-2. Others have shown that pasteurization also renders factor VIII concentrates safe in terms of the transmission of hepatitis B and non-A, non-B hepatitis.[3] Other techniques of viral inactivation, including the extraction of plasma with organic solvents and detergents and heating dry concentrates at very high temperatures, may also be effective for clotting-factor preparations.[4] However, the AIDS epidemic illustrates the possibility that new and deadly infectious agents that are resistant to current inactivation procedures may contaminate the plasma supply in the future.

The article by Schimpf and colleagues points out that pasteurized factor VIII products were prepared as early as 1979. Unfortunately, however, their initial supply was limited, clinical trials of their efficacy against hepatitis had not been completed, and HIV was not identified as the causative agent of AIDS until 1984. Factor VIII preparations that had been heated in the lyophilized state to inactivate hepatitis viruses became available in the United States in 1983. Some physicians favored their immediate use in the hope that the then putative AIDS agent would also be inactivated, but unheated concentrates continued to be used until 1985. The data of Goedert and coworkers show that most patients who are HIV-positive had already seroconverted by 1983. Still, if the heat-treated concentrates had been used exclusively as soon as they became available, some patients with hemophilia might have been spared HIV infection.

Many of the initial reservations about using heat-treated products were related to their cost. Even if the supply had been adequate in 1983, the expense of the heated concentrates would probably have dissuaded many physicians from using them. A similar argument is now raging over the cost of the new ultra-pure factor VIII preparations, including those prepared from plasma by monoclonal-antibody techniques and already licensed and those prepared by recombinant-DNA techniques that are now undergoing clinical trials.[5]

The issue of medical costs is of course not peculiar to hemophilia, but it would be hard to find another disease in which the cost of existing or imminently available therapy is so sharply debated. Although recombinant factor VIII promises to be a step toward an ideal replacement surgery for hemophilia, its expected cost and the current cost of ultra-pure concentrates have led some physicians to question the wisdom of developing new factor VIII preparations. The Health Care Financing Administration has refused to pay for the ultra-pure factor VIII products already available, since there is no clear proof that the newer products are better than the less pure preparations. Some physicians view this stance as shortsighted and have urged the development of new ultra-pure factor VIII products so that clotting-factor concentrates derived from plasma can eventually be avoided altogether. No one could have predicted the tragedy of AIDS in 1978, and who can say that still unidentified but even more dangerous viruses will not contaminate the pools of plasma that are the raw material of blood products? As many as 20,000 donors may contribute to one lot of factor VIII concentrate. Unless new products are widely used, it is unlikely that their costs will decrease, and unless their development is supported, the ideal replacement surgery for hemophilia using recombinant factor VIII is threatened. The factor VIII product of Schimpf and colleagues is clearly an advance, but it is far from ideal. Patients with hemophilia need a factor VIII source that can be used prophylactically. This is the chief promise of the continued development of new and better products.

Patients with hemophilia suffered a major tragedy as a result of the contamination of factor VIII concentrates with HIV. Despite a brutal hereditary disorder and the added burdens of HIV infection and AIDS, patients with hemophilia have persevered and have willingly participated in studies such as those reported in this issue of the *Journal*. There is hope that their contributions will lead to the improved treatment of hemophilia — if not for them, at least for those destined to have the disease in the future. They will experience yet another tragedy if the United States cannot afford to capitalize on the technological advances that hold promise for the ultimate cure of hemophilia.

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Special Communications

The Use of Purified Clotting Factor Concentrates in Hemophilia

Influence of Viral Safety, Cost, and Supply on Therapy

Glenn F. Pierce, MD, PhD; Jeanne M. Lusher, MD; Alan P. Brownstein, MPH, MSW; Jonathan C. Goldsmith, MD; Craig M. Kessler, MD

Treatment of hemophilia, although greatly improved in recent years, continues to be problematic owing to infectious complications of blood product replacement therapy. This report examines the therapeutic options presently available for the treatment of hemophilia, focusing on the potential for repeated viral exposure to influence the progression of infectious disease, decreased risks of viral transmission with blood products produced using newer viral inactivation procedures, higher economic costs of newer blood products, and the current inadequate supply of blood products in the United States.

(*JAMA*. 1989;261:3434-3438)

THE DISCOVERY in 1964 by Pool and Shannon[1] of a cryoprecipitate rich in antihemophilic factor (factor VIII) activity facilitated management of acute bleeding episodes and ushered in a remarkable change in the life-style of persons with hemophilia. By 1970, physicians were prescribing and patients were using partially purified factor VIII and factor IX (Christmas factor) concentrates prepared from pooled plasma to manage even significant bleeding episodes effectively on an outpatient basis. Morbidity previously observed with acute, uncontrolled bleeding into joints and soft tissues was sharply reduced.[2,3]

The concept of comprehensive care of the person with hemophilia was introduced by Levine,[3] and the federally funded treatment center program provided the framework to make comprehensive care a reality in the 1980s for more than half of this country's persons with hemophilia. Comprehensive care has produced tangible benefits to patient and society alike,[4] with a 73% decrease in days lost from work or school, a 74% reduction in unemployment, and a 74% decrease in yearly costs per patient.[5] The survival of patients with hemophilia has increased substantially over the past 20 years as well.[6]

INFECTIOUS COMPLICATIONS OF REPLACEMENT THERAPY

The widespread use of cryoprecipitate and clotting factor concentrates throughout the 1970s was associated with the more frequent emergence of abnormalities in liver function test results and chronic hepatitis due to hepatitis B and hepatitis non-A non-B (NANB) viruses in persons with hemophilia.[7,8] Although the use of these concentrates was initially characterized by minimal symptomatology, mildly elevated transaminase levels, and infrequent progression to chronic active hepatitis or cirrhosis,[8,9] subsequent studies with longer observation periods suggested a small but significant progression to end-stage liver disease and death in some patients.[10-13] Most patients who have been treated with clotting factor concentrates have evidence of previous exposure to hepatitis B and have persistently elevated serum transaminase values despite donor screening for hepatitis B and the recent implementation of surrogate marker testing for NANB hepatitis. The delta agent has also contributed to progression of liver disease in hemophilic carriers of hepatitis B surface antigen.[14] Repeated exposure to nonviral contaminants of clotting factor concentrates, such as immune complexes and high amounts of allogeneic proteins, could also exacerbate the viral-induced hepatitis.

The emergence of significant morbidity and mortality in persons with hemophilia associated with long-term exposure to hepatitis viruses in clotting factor concentrates has lost some impact owing to the emergence of acquired immunodeficiency syndrome (AIDS) in the hemophilic population.[15] The leading cause of death in persons with hemophilia, surpassing bleeding, is now AIDS.[6] As of December 1988, AIDS had devel-

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oped in approximately 7% to 9% of patients with hemophilia seropositive for the human immunodeficiency virus (HIV), or more than 813 persons; more than half had died (B. L. Evatt, MD, D. N. Lawrence, MD, A.P.B., unpublished observations, 1989). Of great concern is that 80% to 90% of persons with severe factor VIII deficiency (classic hemophilia, approximately 8000 to 10 000 persons according to National Hemophilia Foundation and Centers for Disease Control estimates) are seropositive for HIV, the causative agent of AIDS.[4] Fewer patients with factor IX deficiency (Christmas disease, 40% to 50%), mild to moderate hemophilia, or von Willebrand's disease have antibodies to HIV.[4]

The rate of progression to AIDS for HIV antibody–seropositive persons with hemophilia, which was initially considered lower than that observed in homosexual or bisexual men or intravenous drug abusers,[15] is now thought to be similar, as the mean incubation periods for the appearance of AIDS in each high-risk group have been more clearly defined.[16] The progressive loss of immunologic function and circulating levels of CD4 (T-helper/inducer) lymphocytes over several years suggests that despite a mean incubation period of greater than 7 to 8 years, progression to AIDS is continuing to occur.[16,17]

Since the introduction of blood and plasma donor deferral in 1983, the discovery that HIV was inactivated by heat treatment of lyophilized concentrates in 1983 and 1984, and the initiation of donor HIV antibody screening in 1985, continued HIV seroconversion among patients has been greatly minimized.[18-20] However, case reports of HIV seroconversion while using exclusively dry heat–treated concentrates, which were donor deferred but usually not screened for HIV antibody, have recently appeared.[19,21-23]

Table 1.—Summary of Viral Transmission by Factor VIII Concentrates

Method of Viral Inactivation	Transmission: HIV*	Transmission: NANB Hepatitis†	Product‡
Untreated	80%-90%	100%	NA
Dry heat			
24 h, 60°C	1/x§	100%	NA, Profilate HT (dry), Alpha Therapeutic Corp, Los Angeles, Calif
30 h, 60°C	14/x§	100%	NA, Factorate HT, Armour Pharmaceutical Co, Blue Bell, Pa
72 h, 60°C	1/x§	11/13	NA, Hemophil HT, Hyland Division, Baxter Healthcare Corp, Glendale, Calif
72 h, 68°C	0/8‖	2/8	Koate HT, Cutter Biological, Berkeley, Calif
72 h, 80°C	0/22	0/22	Great Britain factor VIII#
Heated in *n*-heptane, 20 h, 60°C	1/x	5/18	Profilate HT (wet), Alpha Therapeutic Corp
	0/13	1/13	
	0/21	. .	
Solvent and detergent (tri-[*n*-butyl] phosphate and sodium cholate)	0/47	0/47	Coagulation factor VIII-SD, New York (NY) Blood Center, American Red Cross
Heated in solution¶: 10 h, 60°C	0/26	0/26	Humate P, Behringwerke, Marburg, West Germany
Vapor heated**: 10 h, 60°C; 1190 millibars; plus 1 h, 60°C	0/55	0/101	Factor VIII, Immuno US, Rochester, Mich
Immunoaffinity purified			
Dry heat; 30 h, 60°C	0/25	0/25	Monoclate, Armour Pharmaceutical Co
Solvent and detergent	0/14	0/14	Hemophil M, Hyland Division, Baxter Healthcare Corp; AHF-M, American Red Cross

*HIV indicates human immunodeficiency virus; and x, an unknown but very large worldwide denominator (ie, over 1000 patients). Operational criteria of the Centers for Disease Control were used to ascribe the probable association of HIV seroconversion with specific factor VIII concentrates.[19] A total of 18 cases were investigated. The 18th patient received products heated in *n*-heptane and dry-heated at 68°C for 72 hours; a single product could not clearly be implicated in the seroconversion.

†NANB indicates non-A non-B. Products with a zero in the numerator for NANB hepatitis transmission should not be assumed to confer absolute protection since the sample sizes in these studies are small, and the guidelines of the International Committee of Hemostasis and Thrombosis for the measurement of liver enzyme concentrations were not rigorously followed in every study (eg, Humate P has been anecdotally implicated in hepatitis B and NANB transmission.[53] Data on the transmission of NANB hepatitis and HIV were obtained from references 15, 18, 19, 21 through 23, and 27 through 31.

‡NA indicates not available. The product is no longer manufactured or sold.

§Other investigators have reported additional HIV seroconversions in patients using factor VIII concentrates. These cases either have not been fully investigated by the Centers for Disease Control or do not fulfill the requirements to association with a particular brand (D. N. Lawrence, MD, oral communication, 1989). These cases include several additional seroconversions that have been reported or are being investigated in patients using products heated at 60°C for 24, 30, or 72 hours.[31] In most instances, the seroconversions reported here were associated with products that were not screened for HIV antibodies; however, at least eight patients received screened concentrates that had been heated at 60°C for 24 or 30 hours.

‖One report has implicated products heated at 68°C for 72 hours in three HIV seroconversions.[52]

¶The Great Britain dry-heat process has not been approved by the Food and Drug Administration for use in the United States.[31]

#No data are available on Koate HS, produced by Cutter Biological.

**Vapor-heated products have not yet been approved for use in the United States. This product was associated with hepatitis B transmission[54]; however, all patients should be vaccinated against hepatitis B prior to receiving concentrates.[19]

VIRAL INACTIVATION METHODS

A total of 18 cases of HIV seroconversion while using virally inactivated concentrates have been reported by the Centers for Disease Control.[19] They have prompted a critical examination of viral-inactivating processes used in the manufacture of clotting factor concentrates by treating physicians, manufacturers, and the Medical and Scientific Advisory Council of the National Hemophilia Foundation (Table 1). Small numbers of HIV seroconversions worldwide have been associated with clotting factor concentrates heated in the dry state at lower temperatures (ie, 60°C) for shorter periods of time (24 to 30 hours, Table 1). Low-temperature heating processes of short-duration are no longer employed as a sole means of HIV inactivation, and other viral-depleting processes are now being used.[19,24] Specifically, manufacturing processes that employ heating in an organic slurry of *n*-heptane, heating to high temperatures (68°C to 80°C) for 72 hours, treatment with a solvent and detergent (ie, tri-[*n*-butyl] phosphate and sodium cholate), heating in aqueous solution, vapor heating, and purification using monoclonal antibody immunoaffinity chromatography coupled with another inactivation procedure (ie, dry heating or solvent-detergent treatment) have been shown to inactivate HIV in vitro.[18,20,25,26] Most of these products have not been implicated in HIV seroconversions in treated patients (Table 1).[19,27-31] However, the number of seronegative patient-years of exposure for some of these concentrates is not large enough to conclude that there is unequivocal HIV safety.

While the HIV margin of safety of these newer coagulation products is significantly better compared with the initially manufactured dry-heated products, transmission of NANB hepatitis has continued to be a problem with most dry-heated products and products heated in *n*-heptane (Table 1).[19,20] Few or no cases of NANB hepatitis have been reported for processes using dry heat at 80°C, heat in the liquid state, solvent-

detergent treatment, and immunoaffinity column purification (Table 1).[19,27-31] These studies have been small and have not had sufficiently long observation periods to assess long-term safety with respect to NANB hepatitis. In addition, in some studies the guidelines recommended by the International Committee of Hemostasis and Thrombosis (biweekly alanine aminotransferase determinations with an increase >2.5 times the upper limit of normal on at least two consecutive occasions) for a positive diagnosis of NANB hepatitis[19,32] were not uniformly followed, potentially missing cases.[33]

Thus, the level of protection against NANB hepatitis has not been conclusively established for newer viral inactivation processes, although it appears to be sharply lower than the 100% rate previously observed with untreated or some dry-heated clotting factor concentrates (Table 1). Viral transmission is also related to other, less-well-studied factors specific to manufacturing processes as well as to the concentration of virus in the donor plasma pool and the viral load administered to the patient (Table 2). In particular, the physical state of the clotting factor (dry, liquid) during the viral inactivation process affects kill of virus (Table 2). Products with lower specific activities, products heated to lower temperatures for less time in a drier state, and those stabilized with chemicals or proteins may give better yields of both clotting factors and viruses. Therefore, the appropriate balance must be addressed between acceptable destruction of product and complete elimination of live virus. Informative data on the effects of stabilizers on viral kill and protein yield are considered proprietary. However, despite some degree of stabilization of protein and virus during processing, newer methods of viral inactivation clearly offer a level of protection substantially greater than previous methods (Table 1).

Unfortunately, most of these newer methods of viral inactivation are not yet approved for use in factor IX concentrates. Available factor IX products are dry-heated for 72 hours at 68°C (Konyne HT, Cutter Biological, Berkeley, Calif), dry-heated for 144 hours at 60°C (Proplex T, Hyland Division, Baxter Healthcare Corp, Glendale, Calif), or heated in *n*-heptane for 20 hours at 60°C (Profilnine HT [wet], Alpha Therapeutic Corp, Los Angeles, Calif). Although, to our knowledge, no HIV seroconversions have been reported in patients using these products, NANB hepatitis transmission remains a significant problem.[33]

THERAPEUTIC CONSIDERATIONS

Good medical practice would suggest that all individuals with hemophilia, regardless of previous exposure to HIV or hepatitis viruses, should receive high-purity products with the lowest possible viral burdens.[34] This argument is supported by several lines of evidence: (1) The established progression to end-stage liver disease may be promoted by repeated viral exposure in patients with preexisting hepatitis. (2) The need exists to prevent all transfusion-related viral infections in previously unexposed patients. (3) The potential transmission of other, as yet unrecognized pathogenic viral agents must be minimized. (4) Repeated viral exposure would promote the progression of HIV infection to symptomatic disease if the cofactor hypothesis is correct.

The cofactor hypothesis suggests that other infectious agents that induce an immune response, in particular, DNA viruses, may stimulate HIV replication in activated T-helper/inducer lymphocytes, causing the destruction of the cell and infection of other previously uninfected cells.[35] Epidemiologic evidence supports this hypothesis: HIV-infected individuals who have other acute and chronic infections appear to lose circulating T-helper/inducer lymphocytes and to progress to AIDS more rapidly.[36,37] Some DNA viruses, such as herpes simplex and cytomegalovirus, can activate HIV in vitro, initiating replication and subsequent destruction of the infected host cell.[38,39] In addition, cytokines that are induced and secreted during a normal immune response stimulate HIV replication in CD4 lymphocytes[40] and in a promonocyte cell line,[41] another cell type that may serve as a significant reservoir for HIV in the body.

Thus, evidence is rapidly accumulating that immune system activation may be detrimental in asymptomatic HIV-infected individuals. Clotting factor concentrates that do not contain HIV can induce a lymphocyte phenotypic picture comparable to that observed, for example, in the immune response elicited by herpesvirus infections or immunizations.[42] This lymphocyte phenotype is compatible with an activated and immunosuppressed state (increased CD8 T-suppressor/cytotoxic cells) and may be related to the observed decrease in cellular immunity among the population of non–HIV-infected patients.[43] Therefore, other viral agents contained in clotting factor concentrates and, perhaps, allogeneic proteins may induce a state of immunologic activation/suppression in the recipient.[44] The recent availability of clotting factor concentrates purified over 3000-fold on monoclonal antibody affinity columns makes the question of immune activation by allogeneic proteins more relevant in HIV-infected individuals. A preliminary clinical trial was initiated,[45] and a large clinical study is under way to evaluate this hypothesis.

Table 2.—Important Variables in Viral Inactivation Procedures and Virus Transmission by Clotting Factor Concentrates

Product Related
Duration of inactivation procedure
Temperature of heat-inactivation procedure
Moisture content
Specific activity at point of inactivation
Addition of stabilizers
Salt
Citrate
Amino acids
Sugars
Alcohol
Heparin
Donor Related
No. of infected donors in plasma pool
Quality of virus-screening assays
Quality of donor referral
Recipient Related
Size of viral inoculum injected into recipient
Doses used for treatment of major vs minor bleeds
Doses used for surgical procedures
Doses used for immune tolerance induction

SUPPLY AND COST CONSIDERATIONS

A major problem in the use of relatively viral-safe, highly purified clotting factor concentrates is their price, which is up to 10 times the 1987 cost of dry-heated concentrates (Table 3). The manufacturers that now offer immunoaffinity-purified products ceased production of lower-priced dry-heated products in 1987.

In 1987, dry-heated products constituted approximately 90% of the total factor VIII consumption in the United States (about 532 million units, Table 3). In 1988, only 125 to 175 million units of dry-heated factor VIII were available in the United States. Since the 1988 demand for dry-heated products was as high as 350 million units (A.P.B., C.M.K., unpublished observations), a significant supply shortage exists.

Due to the shortage of lower-priced products, demand is higher for limited supplies of intermediate-priced products, those heated in solution and treated with solvent and detergent. The remaining products, which are also limited in availability due to decreased yields during manufacture and higher than expected demand, are the higher-priced immunoaffinity-purified concentrates. While the demand for these highly purified concentrates is based predominantly on physician and patient preference, a portion of the demand

Table 3.—Wholesale Prices and Availability of Factor VIII Concentrates*

Process	Price/Unit, ¢		
	Fall 1987	Spring 1988	Winter 1989
Dry heat†	6-9	12	20
Heated in n-heptane	14	25	38
Solvent and detergent	14	28	28
Heated in solution	42-45	42-45	42-95
Immunoaffinity purified	55	55-60	43-65

*Pricing data and the number of total available units of factor VIII concentrate manufactured were obtained by polling 33 randomly selected treatment centers and all clotting factor manufacturers. In 1987, 591 million units were consumed in the total US market. In 1988, 475 million units were available. In 1989, it is estimated that 475 million units will be available. Many variables will have an impact on this estimate, including approvals by the Food and Drug Administration of new products, the final disposition of the withdrawn American Red Cross product under review by the Food and Drug Administration, and the potential for increasing the yield of factor VIII during production.

†The demand for dry-heated product in 1988 was more than double the available supply of 125 to 175 million units.

may be attributed to the lack of availability of other, less expensive options. In addition, the American Red Cross voluntarily withdrew substantial quantities of immunoaffinity-purified product from the market in 1988 owing to procedural irregularities in donor deferral practices, further exacerbating the supply problem.

High prices and low supplies appear to have been influenced in part by worldwide demand for US-produced concentrates and marketing forces designed to recover the substantial developmental costs of these newer products.[46] The plasma industry has traditionally been driven by worldwide demand for albumin, not clotting factor concentrates. Thus, the recent collapse of the worldwide albumin market has also contributed to higher clotting factor prices. Factor VIII has now replaced albumin as the primary demand stimulus for the plasma industry. Patients with copayment requirements, state programs, Medicare, Medicaid, and other third-party payers are experiencing enormous financial pressures as they observe the average treatment costs escalate from $10 000 to more than $60 000 per year.

Several strategies have been implemented to deal with the supply shortfall. A few treatment centers have successfully implemented directed cryoprecipitate donor programs using 1-deamino-8-D-arginine vasopressin stimulation,[47] while others have found it necessary to return to the more widespread use of cryoprecipitate for patients previously participating in self-infusion home therapy programs. In addition, steps to minimize clotting factor usage, including deferral of elective surgery, deferral of immune tolerance induction in inhibitor patients, and use of lower doses and earlier intervention in the treatment of bleeding episodes, have been advocated as temporary measures by the National Hemophilia Foundation.[48]

SUMMARY

The process of normalizing the lifestyle of the person with hemophilia, realized through aggressive outpatient management of acute bleeding episodes, has been compromised by the introduction of potentially lethal infectious diseases transmitted by replacement therapy. The recent availability of products with a significant increase in effective viral destruction is encouraging.

The preliminary evidence suggests that products heated in solution, treated with solvent and detergent, or using immunoaffinity column purification eliminate significantly greater amounts of infectious agents than previously used products. In addition, the concern over immune system activation in HIV-infected persons by other viruses and, perhaps, allogeneic proteins has prompted some physicians and patients to begin using more highly purified products produced using monoclonal antibody affinity columns. However, the high cost and inadequate supply of these products coupled with a relatively small number of patient-years of exposure have complicated treatment decisions. Highly purified factor IX concentrates are not yet available.

Clearly, in this HIV-traumatized population, the goals of total viral safety and protein purity are of major importance. To date, no clinical studies using the newer products have been large enough or have been conducted long enough to provide absolute certainty regarding viral safety or to fulfill the statistical criteria necessary to reach the 95% confidence level for this conclusion. Larger clinical postmarketing studies (phase IV) are needed now on these highly purified products to assess viral safety and the role of cofactors in the progression of HIV disease.

The development of competition between recently introduced immunoaffinity column–purified products as well as the projected clinical availability of recombinant DNA–derived clotting factors in the next 2 to 3 years suggests that the imbalances in supply and cost are temporary phenomena that should be alleviated as we move toward the most viral-safe and alloantigen-safe products available for the treatment of hemophilia. Immunoaffinity column–purified products are considered an interim but significant step in the development of adequate supplies of virally safe and pure replacement products. These goals may be accomplished through the use of recombinant DNA-derived clotting factor[49] and, ultimately, by gene insertion therapy.[50]

With the recent reintroduction of American Red Cross factor VIII concentrate into the marketplace and with improved yields of factor VIII from monoclonal immunoaffinity techniques for purification, the supply shortage of factor VIII concentrate has eased. However, the US supply of concentrate has not yet reached 1987 levels. In addition, the price structure has not yet reflected these improvements in yield or supply of factor VIII concentrate.

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To: MHB
SS
TB
Loker Hovers

THE NATIONAL
HEMOPHILIA FOUNDATION

July 12, 1990

The Honorable John D. Dingell
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives
2323 Rayburn House Office building
Washington, D.C. 20515

Dear Chairman Dingell:

After I completed work on my testimony for the June 13th hearing on the safety of the nation's blood supply, I decided that additional information on the role of the National Hemophilia Foundation (NHF) in dealing with the contamination of the blood supply and blood products by the HIV virus should be given to you and to the Members of the Subcommittee. Although my statement for the record tried to summarize and highlight these events, I believe that this crisis has been so important to the hemophilia community that you need a fuller understanding of events.

As you know NHF is the only national organization in the United States exclusively devoted to serving persons with hemophilia and their families. Since 1948 it has devoted itself to the treatment and cure of hemophilia, and to improving the lives of all those affected through the support of research, education, and other services. Today, we must also address the urgencies posed by HIV disease which has infected approximately 55% of our population.

NHF carries out these programs directly and through coordination with 48 local chapters, 25 federally funded hemophilia treatment centers and over 200 affiliated facilities. Through this network, we fund and participate in a wide range of research designed to improve treatment, develop new technologies and find a cure for hemophilia and AIDS. This network facilitates our educational programs operated for health professionals, persons with hemophilia, their families and the general public to help them manage and understand all aspects of this condition. The Foundation also promotes public policies that not only will benefit those with hemophilia but will also improve the quality of blood for all Americans.

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I remember that day in July 1982 when Dr. Bruce Evatt, Director, Division of Host Factors of the Centers for Disease Control (CDC), called and told me that three people with hemophilia had been diagnosed with a new virus, now known as AIDS. He pointed out the possibility that these cases could be due to some other cause, but he also stated his deep concern that AIDS was a blood borne virus that could be transmitted to other people with hemophilia as well as to other recipients of blood products.

This was only the beginning and at first many health professionals and scientists within the hemophilia community were not sure if these immune deficiencies were due to AIDS. Most people believed that few individuals with hemophilia would actually contract the disease, whatever its cause. Little did we know at the time that HIV infection had already compromised much of the hemophilia community and would eventually affect half of the hemophilia population in the United States. Even though we lacked definitive data to link AIDS to the blood supply, by October 1982 NHF thought that there was more than enough information to warrant initiating new courses of action designed to protect the blood supply. NHF recommended that vigorous steps be taken to exclude donors who were known to be at high risk of contracting AIDS.

Except for Dr. Bruce Evatt at CDC, this position taken by our prestigious Medical and Scientific Advisory Council (MASAC) was not given serious attention. Although we distributed our position paper widely to the leadership of blood collection agencies, and governmental services, we were disappointed that no public policy emerged at that time. We were incensed that there was a lack of willingness to acknowledge the potential seriousness of what was by that time ten cases of AIDS with people with hemophilia.

It was not until January 4, 1983, that the federal government convened a meeting to take action on the problems that seemed to be affecting the nation's blood supply. NHF determined that if no definitive action emerged from the January 4/meeting, we would convene our own panel of experts and issue our own public statement. Our expectations of action at the January 4 meeting were not met, as a number of the blood bank executives objected to any course of action on the absence of definitive scientific information.

Thus, on January 14, 1983, MASAC met in New York City, developed a position on AIDS in relation to blood safety and recommended that it was important to "screen and exclude high risk donors from the blood and plasma supply used in the production of material prepared for the treatment of hemophilia". MASAC also recommended "evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission".

Immediately following this meeting, NHF issued a press release and met with representatives of the commercial fractionation industry, blood banking industry and government agencies. The fractionation industry was immediately supportive of our recommendations, but the blood banking community thought our recommendations were premature because definitive data were lacking. Apparently our message did get through to representatives of the government, because less than two months after that meeting the Public Health Service issued recommendations embodying the concepts of our own statement. This was done in March 1983. Shortly thereafter the volunteer blood banks followed suit. Thus, NHF was the first national body to call for a broad based awareness of the need to safeguard the nations blood supply.

Since that first call from Dr. Evatt in 1982, NHF has been involved with CDC on a regular basis on documenting the spread of AIDS in the hemophilia community. The original epidemiologic workup was done by NHF in collaboration with CDC and confirmed AIDS as a new illness associated with hemophilia. Furthermore, NHF encouraged and completed studies that provided documentation that AIDS is not transmitted through casual contact. From our standpoint this was of critical importance to people with hemophilia in their efforts to survive without discrimination in school and work settings.

NHF was instrumental in encouraging CDC to study the effectiveness of heat inactivation processes to eliminate the risk of transmission of the HIV virus in blood products used by people with hemophilia. Based on these efforts and MASAC's recommendations, the national standard of requiring heat treatment for all blood product concentrates used by people with hemophilia was adopted. Our continued monitoring of seroconversion goes on and has led to the development of even safer methods of inactivating all types of pathogenic blood borne viruses found in blood products.

While our efforts to develop viral free Factor VII have been successful, we have been disappointed in our efforts regarding FActor IX. FDA still has not completed their review of promising new Factor IX products. The result is that these products do not meet the state of the art in viral inactivation.

We have also worked closely with the National Institutes of Allergy and Infectious Diseases to get the inclusion of individuals with hemophilia in their studies of AIDS around the country. We have succeeded in developing an "AIDS Clinical Trial Unit Without Walls" which permits regional hemophilia treatment centers to participate across the country.

Our work in all these areas continues today and much of it goes on with the support and encouragement of Congress and the Federal Agencies. NHF deeply appreciates the support that has been given to it and to the hemophilia community over the years.

I wanted to share these additional thoughts with your because of the importance of the issues you are addressing not only to our community but also to the general public who may from time to time need to use blood products. I would ask that you would include this letter as an addition to my formal statement and incorporate it into the official hearing record.

Sincerely,

Alan P. Brownstein

Alan P. Brownstein
Executive Director

Mr. DINGELL. Dr. Brownstein, the committee thanks you for your very helpful testimony. Dr. Ratnoff, you do not have a prepared statement. Would you like to make a comment at this time, or would you like me to have Mr. Sims ask you several questions?

Mr. RATNOFF. Well, I would like to give just a brief statement.

Mr. DINGELL. Dr. Ratnoff, you are welcome for that purpose. I just wanted to make sure we were proceeding in the way you found best.

Mr. RATNOFF. I had guessed that there would be great reiteration between what I would say and what previous speakers would say, and therefore I wanted to be able to trim my sail.

Mr. DINGELL. Doctor, you are certainly welcome and you are recognized.

TESTIMONY OF OSCAR D. RATNOFF

Mr. RATNOFF. I am a hematologist with about 40 years of experience in the care of hemophiliacs, in teaching about hemophiliacs and in doing research into hemophilia and allied diseases. I have done this in the setting of an academic career. I've been President of the American Society of Hematology. I've been Chairman of the National Institutes of Health Hematology Study Section.

When we talk about hemophilia, we're using the term quite loosely. There are at least two sets of disorders that make up most of the cases of hereditary bleeding disease—classic hemophilia and Christmas Disease. These are clinically very, very similar, but different proteins are defective or missing from the patient's blood.

The severity varies from family to family. It's only in the severe cases that we see the very heavy blood usage that Mr. Brownstein was talking about. Dr. Bruce Evatt of the CDC was kind enough to invite me to the first Public Health Service meeting on AIDS and hemophilia that was held just after the publication in the Morbidity and Mortality weekly report about which you heard.

At that meeting, it was suggested that perhaps the patients with hemophilia would come down with AIDS, had some impairment of their immune defenses, as had been recognized in other patients with AIDS. Armed with this, I went back to Cleveland and did a study which I will try to explain in brief.

Up until the 1960's—about 1963 or so, both hemophilia and Christmas Disease were treated by the infusion of whole plasma. Thus, the patient who came in with a bleeding episode, perhaps bleeding into a joint, might be transfused with the plasma of 8 donors or 6 donors or 4 donors, all volunteers, all presumably healthy.

In the mid 1960's, two types of concentrated clotting factors for treatment of classic hemophilia became available; one, a so-called cryoprecipitate, was a concentrate of anti-hemophiliac factor or Factor VIII that was frozen down, thawed when needed. One might need, for somebody who had bled into a joint, the frozen Factor VIII from perhaps 30 or 40 donors. In the case of a patient undergoing surgery, one might use as many as 600 or 800 donors or more.

These donors, again, were volunteers and the pooling of the plasma fraction, the Factor VIII, occurred only at the time that the

patient was transfused. At about the same time, several commercial manufacturers introduced free 3e-dried concentrates of Factor VIII. That is, Factor VIII would be purified considerably more than in the cryoprecipitates I mentioned, but purified from the pooled plasma of perhaps as many as 20,000 or more donors.

This is truly a case of where one rotten apples gets the whole barrel. These concentrates have the great virtue that they could be frozen, dried and the powder that resulted—this is the same process with which you make a freeze-dried coffee—that powder could then be dissolved at the time the patient needed to be transfused.

This allowed enormously greater mobility for the patient with hemophilia. He could travel away from his home area because he was no longer bound to the hospital in order to get his treatment. Work records improved, school records improved.

It wasn't therefore very surprising that when the epidemic of AIDS appeared, that the greatest possible resistance to change in therapy from these lypholized preparations, the freeze dried preparations to the cryoprecipitates occurred both in the patients themselves and in their treaters. Neither group wanted to see them relapse back to the being tied to a hospital in order to be cared for.

At that time, we did a study which demonstrated, in fact, that my prediction was correct that those patients treated with the freeze-dried fractions of Factor VIII had a very high proportion of impaired immune defenses such as would make them liable for AIDS and to the contrary, those who had been treated with single units appeared to be essentially free of these impairments.

We also did a study to see what effect previous treatment with these freeze-dried materials had on our hemophiliacs, realizing full well that if you don't know a disease exists, you can't protect against it. I happened to have a collection of plasmas from patients and from control individuals that were frozen down in our freezers.

With the help of the CDC, we were able then to study these. We coded these so that people's confidentiality would be maintained; coded them so that the CDC wouldn't know whether they were testing a control/normal or a hemophiliac and what treatment the hemophiliac had had. The result of this study was that beginning in 1980, we were able to find antibodies against the AIDS virus in patients and by 1984, 78 percent of our patients treated with the lypholized freeze-dried material were positive.

In contrast, those who had been treated with the individual donor system of cryoprecipitate did not have any such infection. Since that time, the manufacturers of Factor VIII have learned how better to screen potential donors and reject those who might be transmitting AIDS, but better than that, they have learned how to treat plasma and its fractions—not whole blood, but plasma and its fractions—in such as way as to destroy the virus of AIDS. This is by heat and by the use of organic solvents.

Unfortunately, this has not been all that successful in the treatment of hepatitis, which remains a serious problem. I think I'm going to stop at that point so that I don't reiterate too much of what's been said.

Mr. DINGELL. Dr. Ratnoff, I do not want you to think that we want you to quit. We want you to say what you think is going to be helpful to you and helpful to us.

Gentleman of the panel, there is a vote on the floor that I have to go over and make. I have asked Mr. Wyden to go over early, and he will be back and start things up as quickly as possible, so as to reduce the wastage of your time as much as possible.

I have to go and vote. I will return as quickly thereafter as I can.

The first step, I suspect, when Mr. Wyden comes back will be to commence the process of questions, and then, we will proceed to recognize members in order of their appearance and seniority, according to the rules.

We will, therefore, adjourn for about 5 minutes. Is that acceptable to you gentlemen?

Thank you.

The committee will stand in recess for about 5 minutes.

[Brief recess.]

Mr. WYDEN. Let us come to order.

Chairman Dingell has directed that we proceed. I am going to wait for the ranking minority member, but let us come to order here.

Mr. Eckert, let me begin with you, if I might.

You provided the subcommittee staff with a copy of an article appearing in the September/October 1987 issue of Transfusion. Let me ask of our witnesses—this is a scholarly publication of the blood industry, is it not?

Mr. ECKERT. Yes.

Mr. WYDEN. Let it be entered into the record at this point as Exhibit H by the staff.

[The exhibit follows:]

TRANSFUSION EXHIBIT H

Volume 27 September-October 1987 Number 5

Estimating the risks of transfusion-associated acquired immune deficiency syndrome and human immunodeficiency virus infection

T. A. PETERMAN, K.-J. LUI, D. N. LAWRENCE, AND J. R. ALLEN

The risk of transfusion-associated acquired immunodeficiency syndrome (AIDS) has been difficult to estimate because of the long and variable incubation period. Mathematical modeling suggests there may eventually be 2100 cases among persons aged 13 to 65 who received transfusions between 1978 and 1984. An estimated 12,000 living transfusion recipients of all ages from these years are infected with the human immunodeficiency virus, the virus that causes AIDS. Secondary transmission might be prevented by testing and counseling recipients, but the likelihood of infection in any single recipient is small. TRANSFUSION 1987;27:371-374.

THE FIRST CASE of transfusion-associated (TA) acquired immunodeficiency syndrome (AIDS) was reported in late 1982.[1,2] In the spring of 1983, persons at risk for AIDS were asked to defer themselves from donating blood.[3] Two years later, an antibody test for the virus that causes AIDS was licensed and used to screen all donated blood and plasma.[4] The effects of these interventions on the risk of TA-AIDS have been difficult to estimate due to the long and variable incubation period for AIDS. We present a mathematical model[5] to estimate the number of TA-AIDS cases that will develop in persons who received blood transfusions from 1978 to 1984. We then use this estimate, and the prevalence of human immunodeficiency virus (HIV)* antibody in blood donors in 1985,[6] to estimate the number of recipients who have acquired a TA infection.

Materials and Methods

Patients diagnosed with AIDS before December 1985 and reported to the Centers for Disease Control (CDC) were considered to have TA-AIDS if they met the CDC surveillance definition for AIDS and were at no risk of AIDS other than having a blood transfusion between 1978 and the time of the diagnosis of AIDS.[7,8] If a person received multiple transfusions many months apart, the date of transfusion was considered indeterminant unless the date of transfusion of blood from a donor at increased risk of infection was known. For the purposes of projecting future cases, patients younger than 13 years were excluded because the mean incubation period appears shorter for children.[8] Patients older than 65 years were excluded because their observation time (the time between transfusion and December 1985) was significantly shorter, which led to an imprecise estimate of the total number of cases anticipated in this age group. This short observation time may be due to a decreased recognition of cases early in the epidemic and a shorter life expectancy after transfusion.

Patients were grouped into seven cohorts according to the year of transfusion. Among the k^{th} cohort ($k = 1978, 1979, \ldots, 1984$), N_k infected persons will eventually have TA-AIDS, of whom only n_k had been diagnosed by the end of 1985. The cohort year starts in January, with that month the first time when a case could appear in that cohort. We set TL_k as the number of months between January of the transfusion year and June of 1982, the month when the first case of TA-AIDS was diagnosed. We set TR_k as the number of months between January of the transfusion year and December 31, 1985, the last date of diagnosis included in this study. Assuming that t_{ki} ($i = 1,2, \ldots n_k$) follows an as yet unspecified probability density $f(t_{ki}, \underline{\lambda}*)$, the expected number of N_k can be estimated by:

$$N_k = n_k / \int_{\delta_k TL_k}^{TR_k} f(t, \underline{\lambda}*)dt,$$

where $\delta_k = 1$ if $k = (1978, 1979, \ldots, 1982)$, and otherwise $\delta_k = 0$. As shown previously,[5] when assuming $f(t, \underline{\lambda}*)$ to be the Weibull model, the model derived using the maximum likelihood estimation technique described the observed data well.

In the recipients who received transfusions between 1978 and 1984, some cases would have been missed—m_k ($k = 1978, \ldots 1982$)—because the first case of TA-AIDS was not recognized until June 1982. This number m_k can be estimated by N_k times $\int_0^{\delta_k TL_k} f(t, \underline{\lambda}*)\ dt$. Therefore, the expected number of cases that will be diagnosed after December 1985 for the K^{th} cohort is equal to $N_k - n_k - m_k$. Ninety percent confidence intervals were calculated for each cohort using the delta method.[9] To compensate for the patients with indeterminant dates of transfusion, the expected number of cases and the confidence intervals both

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* The AIDS virus is also known as the human T-cell lymphotropic virus type III (HTLV-III) or the lymphadenopathy-associated virus (LAV).

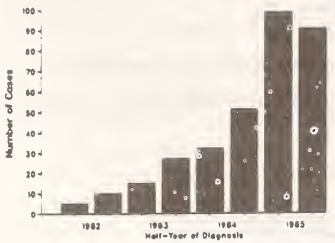

FIG. 1. Cases of transfusion-associated AIDS by half-year of diagnosis.

were divided by the proportion of cases (0.786) for which the date of transfusion was known.

The number of infected recipients of all ages was estimated by using the following assumptions: 1) Eighteen million units of red cells, platelets, plasma, and whole blood were transfused each year (*N*. Holland, personal communication). 2) Units that test positive for anti-HIV would all transmit infection if transfused.[10] 3) The rate of seropositivity among donors in 1984 was the rate found when screening began in 1985 (0.04%).[9] 4) Each infected unit was transfused to a different person. 5) The risk of infection in previous years was proportional to the risk of TA-AIDS estimated by the model. To estimate the number of living transfusion-infected recipients, we estimated that 60 percent of all recipients have died of their underlying illness.[11]

Results

The epidemic curve for TA-AIDS shows a continued increase in the number of cases (Fig. 1). When cases are sorted by the year the patients received their transfusion, the risk of infection in each year is more easily assessed (Fig. 2). However, the total number of cases for each transfusion-year cohort is not known because cases continue to be reported in recipients from each year. In addition, some cases were apparently missed in the years before the first case of TA-AIDS was described.

The model estimates the number of cases that were

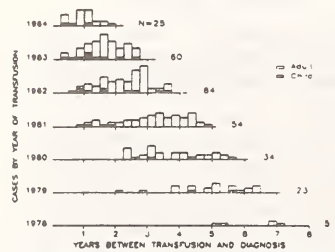

FIG. 2. Incubation periods for cases of transfusion-associated AIDS reported as of April 1986 by the year in which the patients received transfusion.

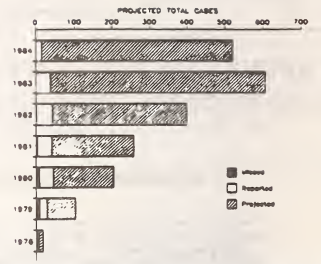

FIG. 3. Projected transfusion-associated AIDS cases in adults aged 13 to 64 years who received transfusions from 1978 to 1984 by the year in which they received transfusion.

missed and the number that will be diagnosed in the future for each of the cohorts (Fig. 3). The cases currently reported represent only 9 percent of the cases that we project may develop in recipients of transfusions between 1978 and 1984. The model predicts a total of 2100 AIDS cases in persons 13 to 65 years old who received transfusions in these years. This estimate is based on relatively short periods of observation, especially for the 1984 cohort; therefore, summing the 90 percent confidence intervals for each cohort yields a wide confidence interval (445–∞).

If infections are distributed in the same proportions as the number of cases that the model projects for these years—ie, 7200 infections were transmitted in 1984 (18,000,000 units × 0.04% seropositive)—an estimated 29,000 infections were transmitted in the period 1978 to 1984 (Fig. 4). If 60 percent of these patients have died of their underlying disease, then approximately 12,000 living transfusion recipients of all ages are infected.

Discussion

The long, widely variable incubation period for AIDS makes it difficult to estimate the magnitude of the problem of TA-AIDS or the effects of interventions to stop transmission. Previous estimates of the

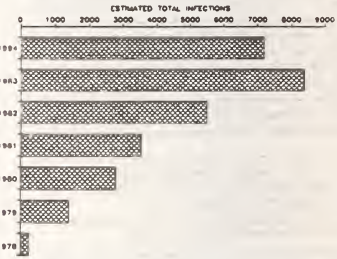

FIG. 4. Estimated transfusion-associated HIV infections in all patients who received transfusions from 1978 to 1984 by the year in which they received transfusion.

risk of TA-AIDS were based on the cases reported at the time of the estimate,[12] but the incubation period is so long that most of the cases have still not occurred. The model estimates that the total number of cases in persons who were 13 to 65 years old at the time of transfusion in 1978 to 1984 will eventually reach 2100, about 11 times the number reported by April 1986. Since the model is based on a relatively short observation period, the estimate cannot be exact. However, it is clear that the number of cases will be much higher than that currently reported.

Even this projected number of AIDS cases underestimates the impact of TA HIV infection since it does not include persons with AIDS-related conditions or asymptomatic infections. We estimate that 29,000 transfusion recipients of all ages from these years received a unit of blood infected by HIV and that approximately 12,000 are still alive. These people are at risk for AIDS or AIDS-related conditions and may also transmit infection to others.

In several cases reported to CDC the only apparent risk was sexual or perinatal exposure to an asymptomatic, infected transfusion recipient. The number of secondary transmission cases to be expected from the 12,000 infected recipients is difficult to estimate. Most recipients are beyond their reproductive years (70% of red cell transfusions are given to people older than 50 years)[13] and many are no longer sexually active due to the illness that caused them to require the transfusions. Nevertheless, some secondary transmission might be avoided by identifying and counseling infected transfusion recipients.

Blood collection agencies now notify hospitals that they received units of blood from donors who later tested positive for anti-HIV. The recipients of that blood may then be counseled by their physicians and tested for exposure to HIV. This system of tracing previous recipients has the advantage of notifying some recipients with a likelihood of infection. However, other asymptomatic infected recipients will not be identified if their donors have not donated since the antibody testing began. Although the overall risk of infection is low for recipients transfused from 1978 to 1984, recipients of unscreened blood from areas with a high incidence of AIDS may benefit from counseling and HIV antibody testing, especially if they are in social situations where they may transmit infection.

Donor self-deferral resulted in significant changes in the blood donor population after its initiation in 1983. The number of male donors aged 21 to 35 in New York City decreased by 12 percent.[14] The percentage of donors with other sexually transmitted infections also declined. In Atlanta, the number of units with positive syphilis serologic findings declined by 37 percent;[15] the number positive for hepatitis B surface antigen declined by 25 percent there and by 57 percent in Philadelphia.[15,16] However, at the same time that many people at risk were deferring from donating blood, the prevalence of HIV infection was increasing.[17] Although the risk was lower than it would have been without self-deferral, the risk of TA-AIDS is higher for recipients who received transfusions from 1983 to 1984 than for recipients from 1982 (Figs. 2 and 3).

No AIDS cases have been reported in recipients of screened blood, but the incubation period of TA-AIDS is so long that we would have expected only a few cases to have been reported by April 1986, even without screening. One case of HIV transmission by screened blood has been reported.[18] In this case the donor had apparently been infected for only a few weeks when he donated, and detectable antibody had not developed. Four additional reports have been received by CDC in which transmission had apparently occurred via screened blood.

The risk of acquiring a TA infection from a unit of screened blood can be estimated by using the seropositivity rate in blood donors as an approximation of the prevalence of infection and an estimate of the sensitivity of the antibody test. The actual sensitivity of an ELISA test in detecting infection is not known, but it is probably close to 100 percent for persons who have been infected for more than a few months; however, most persons who have been infected for only a few weeks will have negative test results. If the prevalence of infection in donated blood is now 0.013 percent[19] and sensitivity of an early research test of 96 percent[20] is used to make the calculation, then 5 units out of 1 million could be infectious. The current sensitivity of the licensed tests is believed to be much higher. Although the actual prevalence of infection in blood donors will vary in different parts of the country and the sensitivity figure is only an estimate, the risk remains low over a reasonable range of prevalence and sensitivity. Nevertheless, work to lower the risk further should continue.

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Mr. WYDEN. In this article, and I quote, the authors state, "We estimate that 29,000 transfusion recipients of all ages from these years received a unit of blood infected by HIV and that approximately 12,000 of these are still alive. These people are at risk for AIDS or AIDS-related conditions and may also transmit infection to others."

Mr. Eckert, is this estimate based on data compiled by the CDC?

Mr. ECKERT. My recollection of that study, Mr. Wyden, is that it is based on a mathematical estimation procedure. I think they took certain data that were known to them and made an estimate of what the outcome would be.

Mr. WYDEN. Let me also note, because this document is being placed into the record, that at the bottom of page 371, it states that it was based on the AIDS Program, Division of Viral Disease, and Division of Host Factors, Center for Infectious Diseases, Centers for Disease Control.

Does this estimate, Mr. Eckert, to the best of your knowledge, include hemophiliacs?

Mr. ECKERT. I do not think it does.

Mr. WYDEN. During the October of 1989 meeting—and this was the meeting of the FDA Blood Products Advisory Committee, Mr. Eckert, there were extensive discussions regarding the reentry of donors, were there not?

Mr. ECKERT. Yes, that is right.

Mr. WYDEN. Explain for us, if you would, what donor reentry is.

Mr. ECKERT. Well, Mr. Wyden, this is a procedure whereby a donor who has been deferred by blood tests is later reentered or allowed to go back into the donor pool based on certain criteria, based on new tests, based on coming back to the blood bank after a period of time, additional testing having been done.

I cannot recall to you today the precise rules of that, what they call the algorithm, which is the sequence of decisions that are required for that to occur. It is quite complex, and the issue is that it was being—a new algorithm, a modified algorithm was being proposed that day.

Mr. WYDEN. Let me ask you this—now, this data, according to the article, was based on the period between 1978 and 1984. The article was written in Transfusion in the fall of 1987. Is there any estimate as to how many people, donors, might be involved, as it relates to this population?

Mr. ECKERT. The donors of the 12,000 people who are presumably still alive and infected? I have not seen any.

Mr. WYDEN. Is there significant industry concern about this matter? Has there been extensive discussion among the industry as to how to handle this group?

Mr. ECKERT. Well, I am not the person to ask that of, Mr. Chairman. I am not privy to the industry's debates.

Mr. WYDEN. Who would?

Mr. ECKERT. I think it would be suitable to ask the industry that question.

Mr. WYDEN. How about some of our other panel members? Has there been significant industry-wide discussion about the possibility of those individuals cited in the 1987 Transfusion study reentering as donors?

Dr. Engleman?

Mr. ENGLEMAN. Any donor who is identified as a source of HIV is permanently deferred. That does not guarantee that that individual will not try to donate again, but it is about as well as we can do in terms of permanently deferring those people who are infected.

Mr. WYDEN. Have there been steps to ensure that this population group is not donating?

Mr. ENGLEMAN. In my State, the State of California, the names of individuals who test positive for HIV is sent to the State, which has a statewide registry to prevent this kind of incident.

Mr. WYDEN. Do you believe that that kind of check exists nationwide?

Mr. ENGLEMAN. I cannot say with certainty. I believe it exists for most of the Nation.

Mr. WYDEN. Mr. Eckert?

Mr. ECKERT. I am sorry, Mr. Chairman. I did not realize that you were asking what is the—what are the rules by which these people could become blood donors. I did not understand your question.

Mr. WYDEN. I will ask other members on the panel.

Mr. Brownstein, when one reads of a study like this in an authoritative blood journal and then Mr. Eckert describes the reentry of donors, the first question that comes to mind is whether or not there are airtight procedures in place to prevent further donations, and I am still not clear as to whether there are.

Mr. Brownstein?

Mr. BROWNSTEIN. Well, aside from the 12,000 donors that you made reference to with respect to HIV, we do not think it is a good idea for blood donors to be donating blood, because blood—I mean blood recipients to be donating blood, and I think, in many areas—and I do not have the exact facts, but blood recipients are deferred from donating blood for a period of time, and I do not know if this is based on State or national recommendations, and anyone who receives blood can be subject to receiving any number of viruses that, in turn, can be passed on.

Mr. WYDEN. The subcommittee staff has been told of a blood-industry meeting held in San Francisco at which FDA personnel spoke. At this meeting, a senior inspector of the FDA was asked what FDA would require of the blood industry if donors tested positive for the hepatitis B core antibody. This inspector reportedly stated that the donor should be deferred and the blood should not be used for transfusion.

In the afternoon, according to what the subcommittee has been told, the senior FDA official from Washington got up and told industry representatives that they had been misadvised and that donors testing positive for the B core test did not have to be deferred and the blood could be used.

Let me ask you, Dr. Engleman, and you, Dr. Conant, whether you are familiar with this incident and whether you could provide any details.

Dr. Conant?

Mr. CONANT. I am not familiar with the incident you cite, but it is strange, and let me try to clarify it by pointing out what the blood industry has been doing for years.

It is known that an individual whose behavior put them at risk for getting hepatitis B could acquire a number of other diseases, cytomegalovirus, as Dr. Engleman mentioned earlier, and AIDS. The blood industry has known that and has acknowledged it for years, and if a donor goes in and gives a history of having had hepatitis B, that donor will be deferred and deferred permanently, but only half of us who have ever had hepatitis B know that we have had the disease.

Many people are infected with hepatitis B, recover, and have no clinical symptoms. Those individuals will test core positive, even though they have had no symptoms, and yet, the blood industry will take blood from those individuals—or would, up until 1986—because they were not doing the core test to eliminate you.

In other words, they had a way of being more stringent in their evaluation, rather than just the patient's history, and they were not using it.

Mr. WYDEN. Dr. Engleman?

Mr. ENGLEMAN. I, too, am not familiar with that specific incident, although I certainly heard of it.

Mr. WYDEN. Pardon me. Where did you hear of it?

Mr. ENGLEMAN. I was aware of it in the last 6 months, I cannot tell you where I heard of it.

But, the point I was trying to make is that the issue of using the hepatitis B core antibody test is one that our industry failed to apply soon enough. Not only because of its documented value as a surrogate test for AIDS, but also because we have known for some time, even before the AIDS epidemic began, that—that that test, had it been used, would have reduced the incidence of non-A/non-B hepatitis; which is a much more common problem than even hepatitis B in the transfusion recipient.

It was not until 1986 that the core antibody test was recommended for wide-spread use; and it is a pity, because it would have worked.

Mr. WYDEN. Do any of our other panel members have any information on that?

I am also concerned about the fact that one hand of the FDA says one thing in the morning and the other hand of the FDA says something else in the afternoon. I gather, Dr. Engleman, this report is fairly widely known throughout the blood industry?

Mr. ENGLEMAN. Well, I think—I think it should be emphasized that the entire industry is using the core antibody test, and a positive test does result in the deferral of a donor who tests positive.

So, regardless of what that official might have said, and it is regrettable, the industry is using the test finally.

Mr. WYDEN. Let me see if my colleague can get something in before our vote.

The gentleman from Virginia.

Mr. BLILEY. Dr. Conant, during and after January 1983's CDC meeting, the blood industry suggested further studies of surrogate tests, to identify the donors in high-risk groups for AIDS.

Indeed, as Dr. Bove's letter states, one of the apparent strategies to avoid unwanted testing requirements was to buy time by studying the matter to death.

One study conducted by the Irwin Memorial Blood Bank in San Francisco, reported that the rate of anti-B core positive among homosexual donors was not very high; and also was not very different than the rate among heterosexual donors.

What was wrong with this study; and what would you have expected the results to show?

Mr. CONANT. I would characterize the study as poorly—poorly executed.

And let me take a moment and explain to you how it was done and what it showed, because that study was used by the industry to say that they didn't need to do surrogate testing.

They decided that they would go through San Francisco and decide by zipcode, which areas had large gay populations and which areas had low gay populations. Dr. Perkins, who ran the blood bank, was told, erroneously, that 100 percent of the people living in the Castro District of San Francisco are gay. That's not true, but it is a very high proportion. He was told that numbers of people living in other areas of San Francisco were basically heterosexual.

It was known at that time, known and accepted, that if you go and test a heterosexual population, 5 percent of them will test positive for hepatitis B core; and yet 75 percent of gay men were testing positive to core.

So the hypothesis of the study is, if we look in a straight community, 5 percent should be core positive; if you look in a gay community, 75 percent should be core positive.

He did the study, they linked the test to zipcodes and they found that in the straight communities, 5 percent were core positive. But in the Castro District, 9 percent were positive.

Now there's something wrong. You, as a scientist, expect to find 75 percent and you find 9 percent.

Dr. Perkins has testified that they didn't believe the data; but at that point, they decided that "those kinds of people who would get AIDS wouldn't come to the blood bank," they threw out the data and they quit doing surrogate testing for another year.

The tragedy is that of the 10,000 donors they tested, they lost, or do not have the data on 2,000 of them. In other words, they lost 20 percent of their data, which may have well represented the group under scrutiny from the Castro.

We don't know what happened to the data. But it was a poorly done study. Any good scientist, finding that the results of his experiment did not agree with his hypothesis, would go back and continue to test it until he could explain the discrepancy.

Mr. BLILEY. Thank you.

Since I mentioned Dr. Bove's letter, I would like to ask unanimous consent to include it in the record at this point, as Exhibit C.

[The document follows:]

January, 1983

EXHIBIT C AGENDA ITEM B1

PM-19 ED 9/27/83

Report to the Board
Committee on Transfusion Transmitted Diseases

The major report of your Committee on Transfusion Transmitted Diseases has been issued as our recommendations to the Association. These few additional paragraphs are more my current views and concerns than a formal committee report. Nonetheless, because of my recent experiences I am anxious to share some thoughts with you.

The report that we have submitted to our members is, in my view, appropriate considering the data at hand. Since we met, however, an additional child with AIDS has been admitted to a Texas hospital. At birth the child had received seven transfusions, one of which came from a donor who now seems to have AIDS. This case increases the probability that AIDS may be spread by blood. Furthermore, the CDC continues to investigate the current cases aggressively and may even have a few more. While I believe our report reacts appropriately to the data at hand, I also believe that the most we can do in this situation is buy time. There is little doubt in my mind that additional transfusion related cases and additional cases in patients with hemophilia will surface. Should this happen, we will be obliged to review our current stance and probably to move in the same direction as the commercial fractionators. By that I mean it will be essential for us to take some active steps to screen out donor populations who are at high risk of AIDS. For practical purposes this means gay males.

The matter of arranging an appropriate screening program is delicate and difficult. We have had excellent cooperation from individuals in the gay community and our deliberations have been made easier by their knowledge and ability to help us. I have no doubt that they will continue to support us and, should we need to be more aggressive in this area, will help us do it in a way that is socially responsible.

Blood banks that wish to sell plasma for further fractionation already face the need to do something. Perhaps our Committee should prepare guidelines with suggested wording for them to use. We are reluctant to do this since we do not want anything that we do now to be interpreted by society (or by legal authorities) as agreeing with the concept - as yet unproven - that AIDS can be spread by blood.

All in all this is a knotty problem and one that we will not solve easily.

I want to make a few comments about the process by which our joint document developed. We spent a great deal of time and energy and did the best we could in attempting to reach a consensus. The difficulty was to get AABB,ARC, CCBC and all the other groups to adopt a postion which was acceptable to each other. It was impossible to have a small meeting; everybody wanted to attend. When we got the group together we were able to hammer out a statement that pleased the attendees. Unfortunately, the statement had to go through several iterations with our own Board and the Boards of the other involved organizations. In

all probability these modifications resulted in a better statement, but the process of getting these changes incorporated and run back and forth through the three organizations was difficult. We have had a good start at working together on this and we hope to keep it up. The mechanism was a little less smooth when it came to releasing the statements and the public relations that went with it.

I hope that we are equipped psychologically to continue to act together. I have been in contact with ARC (Dr. Katz) and CCBC (Dr. Manitove) and believe that the three of us can, together, work out whatever new problems may arise. We plan frequent conference calls to keep each other informed.

I want to comment about the Committee. They worked well together and I was particularly pleased with the input of advisory members. Having individuals who are not associated with the blood banks nor a traditional part of the blood banking community proved most useful to us. Their comments and suggestions were excellent. In a like manner, we were helped by participants from the National Gay Task Force. As we continue to react to the various challenges before us, I am sure that their help will be essential. Finally, let me acknowledge the help from the Central Office and, in particular from Lorry Rose.

No immediate end to the publicity is in sight and we will get continued calls for us to act more aggressively. We need to do whatever is medically correct. In addition, we may have to do a little more, since we are accused of burying our heads in the sand. We are not being helped by the spate of publicity about this illness, but will continue to react responsibility to whatever scientific and medical information we have.

Joseph R. Bove

Joseph R. Bove, M.D., Chairman
Committee on Transfusion Transmitted Diseases
American Association of Blood Banks

JRB:tmf

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Mr. BLILEY. If the 2,000 results that were lost were all or nearly all positive, would the study results be more—what would—we would expect?

Mr. CONANT. Yes, sir. The answer to that is yes. But good science would not condone speculation.

Mr. BLILEY. They did not redo the test?

Mr. CONANT. But clearly, you do not accept the results of a study that important, when you have lost a fifth of the data.

Mr. BLILEY. But yet, despite the obvious problem with the study, it was cited as an argument against anti-B core testing; wasn't it?

Mr. CONANT. Yes, sir. There were only three studies done: one in New York, one in San Francisco, and one in Arizona. Each of the three was flawed in a different way. This was one of the seminal studies that was cited that core testing was not necessary.

Mr. BLILEY. That leads me to my next question.

Are any of the panelists familiar with the anti-B core results that were study that the New York Blood Center did, which asked donors to indicate whether their blood should be used for research only, or for transfusion?

Mr. CONANT. Yes, sir. I am very familiar with Dr. Pendyke's study.

Mr. BLILEY. Was there something wrong with his methodology?

Mr. CONANT. Hers. Yes, sir.

In Dr. Pendyke's study, the—the interesting thing is that the way that study was constructed, her donors came in and they were educated about AIDS far more intensively than other blood banks; and then they were told to indicate whether their blood should be used for transfusion, indicating that they thought they were safe to give blood, or whether their blood should be used only for research; indicating that they thought that they might have a risk group, such as homosexual behavior or IV drug use.

They found that high-risk donors coming in, well educated, did exclude because there was a high prevalence of hepatitis B core positivity. But they also found that very few high-risk donors were coming in.

So while the conclusion of the study was that hepatitis B core testing would be a useful way to pick up high risk donors, they pointed to the fact that there were very few high risk donors coming in and they said that their public education to get people at risk to self-defer was enough and they did not need to do more.

But what they didn't point out, except in the fine print; if you only carefully read the article, was they had had an intensive media blitz in New York preceding—immediately preceding the study, and going on during the study, so that high-risk donors were being intensively educated right at that point.

Now they did not continue that media blitz after they did their study; and other blood banks around the country did not have that type of media blitz.

Furthermore, they showed during their study, that as a result of the media blitz, the number of male donors from New York City dropped by 12 percent. So, other blood banks could have looked at what they were doing. Irwin Memorial in San Francisco could have said: have our male donors dropped after 1983 as an indication that

people were learning that there was AIDS in the blood supply and they should not come in?

The blood banks did not do that.

So, they had a way of testing the results, they did not do it. The Pendyke Study shows that core testing would be effective. They erroneously concluded it was not necessary.

Mr. BLILEY. Thank you, doctor.

Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentleman.

Gentlemen of the panel, some questions.

Professor Eckert, according to scientific studies cited in your 1985 book, entitled Securing a Safer Blood Supply, page 18, between 210,000 and 381,000 persons could be expected to contract hepatitis from blood transfusions annually; most of which was non-A, non-B type hepatitis; is this correct?

Mr. ECKERT. Pardon me, that is correct, Mr. Chairman. That book was published in 1985, so that was an estimate, based on—the source that was used for that estimate would have been pre-1985.

Mr. DINGELL. Now in 1985 there was no direct test for non-A/non-B hepatitis, was there?

Mr. ECKERT. Yes, that's correct.

Mr. DINGELL. But there were several surrogate tests available at that time which could identify a significant percentage of non-A/non-B hepatitis, isn't that so?

Mr. ECKERT. That's correct.

Mr. DINGELL. Now the anti B core test had been available since 1976. What is your belief with regard to the primary reason as to why the blood industry did not adopt this test and thereby reduce by thousands the number of cases of non-A/non-B hepatitis passed via transfusions each year?

Mr. ECKERT. Well, the literature that I read, the trade literature that I read, was always emphasizing the number of donors that they would lose and these tests, remember, were not perfect. They would reject some safe blood and the industry was very concerned about the cost of replacing and the effort and the cost of replacing the donors who would be rejected by the test.

Mr. DINGELL. How would you and the other members of the panel weigh out that cost versus the risk to recipients of this blood of receiving non-A/non-B hepatitis or other diseases by reason of failure to appropriately and adequately test that blood?

Mr. ECKERT. Well, Mr. Chairman, as I said in my statement, I quoted a cite of the study that was published in 1984 in the Journal of the American Medical Association which analyzed the costs and benefits of the ALT test, which is a somewhat different laboratory test than the hepatitis core antibody test, and that study, that analysis concluded that surrogate testing with the ALT test would be cost effective, taking into account the extra solicitation of donors that would be required but before considering the lost wages of patients, and of course if somebody gets sick from one of these diseases and has a hospitalization and has some period out of work the lost wages are an absolutely relevant factor that should be taken into account.

The full studies for that period haven't been done but it is my estimate and based on very straightforward, back of the envelope

sorts of calculations that I have done I think if the full studies are ever done it will be shown that core testing and ALT testing would have been cost effective for hepatitis alone to say nothing of their value as a surrogate marker for AIDS .

Mr. DINGELL. Dr. Conant, I observed you nodding one way or another. Do you want to tell us what your thoughts are on that, please, sir?

Mr. CONANT. Mr. Dingell, as a practicing physician if I had said to you, you know, we're going to have to start doing core testing. It's going to cost about $5 a unit to do every unit and probably for every patient with AIDS we identify we'll have to throw away 20 units that weren't infected with AIDS so that is going to add another $5. Which would you rather have, a transfusion at $100 or a transfusion at $110 which has had the best screening we have available for AIDS ?

From my experience from 28 years of practice I don't think I would have a single patient who would have said, oh, I'd rather have the cheaper blood.

Mr. DINGELL. I concur. Any comments of the panel?

Dr. Ratnoff, you were having some small chuckle at this.

Were you going to give us a comment?

Mr. RATNOFF. Well, I presume that the inertia on the part of the blood banking community, of which I am not a member, may have been much more the question of the decrease in the number of potential donors than in there being concern about the cost. If you don't have donors to give blood for patients, it doesn't matter how much it costs if there isn't any blood and I really shouldn't be speaking for them because this is way out of my knowledge except from hearing them at some of these meetings but I would think it was that which motivated the inertia about surrogate testing, fear that they would not have the blood supply that was needed for the care of patients.

Mr. DINGELL. I gather this would be generally the consensus among the panel. Mr. Brownstein?

Mr. BROWNSTEIN. I, too, do not have the knowledge directly of what the blood bankers, how they felt about it except that I heard reference to the costs that are involved and that is why in my testimony earlier I made the representation that where new blood products are provided or for that matter wherever new safety measures are provided there needs to be the public commitment to support whatever the cost may be when it becomes a matter of a question of whether we are going to spend the dollars or have safety.

Mr. DINGELL. Dr. Engleman, did you want to add any comment?

Mr. ENGLEMAN. Well, I think that a number of reasons were cited, certainly when the subject of hepatitis B core testing as a potential surrogate for AIDS was considered. It was cost, dollar cost, loss of donors. It was concern about the fact that the test wasn't perfect so in addition to identifying high risk individuals there were going to be some individuals who were identified who probably were not high risk individuals.

The problem though I have with all of these concerns is that by comparison to the overwhelming concern there should have been about protection of the blood supply these pale and it's extraordinary to look back in retrospect, at least in my view and wonder

how the decision possibly could have been made, even given the fact that there was going to be some loss of donors, et cetera, because when in fact the tests were incorporated in 1986 we did not experience any massive blood shortages.

All of that could have been predicted on the basis of the small percentage of donors that would have been affected in the first place.

Mr. ECKERT. Mr. Chairman, there were estimates that there were 3, 4, 5, 6 percent. It varied from publication to publication and person to person but that was the realm of the number of donors who were expected to be rejected by these tests, although conceivably the more tests you use, the more donors would be rejected but then also it's true that some donors are going to be rejected by both tests so I think the amounts that were being under discussion were fairly small.

If I could offer a somewhat different perspective on this problem, it might be useful for all of us to just think hypothetically for a moment as to what a consumer might pay to reduce the risk of hepatitis from say one in ten, which was a common estimate of the industry, hepatitis of all forms from transfusion, from one in ten in the year before surrogate testing to let us assume surrogate testing cut it by half.

Hepatitis can be a really mean disease. What would a well-informed consumer do if the cost is maybe $3, $4, $5 extra per unit of blood?

Well, we haven't asked many consumers. We would all have to just play this mental game in our minds to see what we would do under the circumstances, but we know that most people buy fire insurance on their houses. For most people, the likelihood of a fire on somebody's house is trivial any given day or year in most communities but people buy it. Most consumers buy it and they have a lot of their assets tied up in their homes.

People who work have a lot of assets tied up in their human capital too and my guess is that most consumers if granted the choice would have been willing to pay this relatively small amount.

Mr. DINGELL. Now, gentlemen, without objection the Chair places in the record Exhibit F, the sworn affidavit from a lawsuit in New Jersey of Dr. Thomas Asher, Ph.D. in Bacteriology with some 30 years of experience in the blood community. Dr. Asher is the Chairman of the Board of HemoCare, manufacturer of blood products and was a member of the Board of Directors of the American Blood Resources Association from 1976 through 1989.

In paragraph 8 Dr. Asher accounts his attendance at a November, 1982 presentation by Dr. Bruce Evatt of CDC at which CDC presented data showing AIDS carriers could be identified by surrogate tests. This is again the same type of data we have been discussing and the CDC presented it to a larger group at the January, 1983 meeting, already discussed here.

Dr. Asher makes this statement, and I quote, "Published data had demonstrated that the major risk group for AIDS, i.e., male homosexuals, also had a very high incidence of history of hepatitis B. This had been demonstrated by numerous surveys over the previous 3 to 5 years which had been established in public health literature."

In paragraph 9 Dr. Asher recounts how his company decided to implement a surrogate test for abnormally low lymphocyte levels as well as requiring donors to state their sexual preference and then to examine them for swollen lymph glands.

He then makes this statement, and I quote: "By 1984 blood which was not tested by one of the following three tests, T-4/T-8 cell test, lymphocyte count, or hepatitis B core antibody, was unreasonably dangerous. To not test blood by any of the above tests was unreasonable and negligent."

[The document referred to follows:]

EXHIBIT F

SUPERIOR COURT OF NEW JERSEY
LAW DIVISION: BERGEN COUNTY
DOCKET NO: L-37610-88 MM

WILLIAM AND ROSLYN SNYDER

Plaintiffs,

vs.

BERGEN COMMUNITY BLOOD CENTER et. als.,

Defendants.

AFFIDAVIT
OF
THOMAS M. ASHER

I, Thomas, M. Asher, being of sound mind and full age, based upon my oath, do hereby certify as follows:

1. My formal educational background is as follows: B.A., (Bacteriology), UCLA, 1947; M.A., (Microbiology), UCLA, 1948; Ph.D., (Bacteriology), University of London, 1950.
2. My academic/public health employment experience includes three years as a memeber of the facility at the University of California, Berkeley and six years in the U.S. Public Health Service, Center for Disease Control, Atlanta Georgia.
3. My first commercial/practical employment experience was the eight years spent at Hyland Laboratories, the world's largest fractionator of human plasma products,

having a variety of responsibilities including Director of Quality Control and General Manager of the Blood Banking Reagents Division.

4. I have co-founded two biomedical companies, both involving procurement and processing human blood products either for resale to other biological manufacturers or directly to hospitals for human transfusion. My responsibilities included that of being the company official responsible for Federal FDA and California Department of Health licensure. A more detailed description of my experience and responsibilities are to be found in the attached Curriculum Vitae (Exhibit A).

5. I have working knowledge of the operation of highly specialized blood banks on a national level. While exercising my varied responsibilities I have dealt with the many aspects of blood banking and have working knowledge of the risks of transfusing potentially infectious blood products. I have formulated donor screeening and surrogate testing standards for autologous, designated, and homologous blood products.

6. From 1976 through 1989, I was a member of the Board of Directors of the American Blood Resources Association (ABRA) as well as a member of it's Executive committee. I have made presentations on technical and political factors of the blood industry to the Presidential Commission of the HIV Epidemic and to the Subcommittee

on Oversight of the House of Representatives, Ways and Means Committee.

7. In mid 1982, I had become aware of the potential for blood products to transmit AIDS as a result of U.S. Public Health Service, Morbidity and Mortality Weekly Reports. In November of 1982, I personally attended a presentation given by Doctor Bruce Evatt of the United States Public Health Service, Center for Disease Control (CDC) to the ABRA membership in which he presented data generated at CDC showing a link between many surrogate laboratory tests and AIDS carriers. My original copy of this data as distributed by Dr. Evatt at the time is attached at this Affidavit as Exhibit B.
His data resulted in significant concern on my part and that of other members of the blood industry who were seated with me at the first presentation.

8. As a result of information gained through reading the reports mentioned above and studying Dr. Evatt's data, I gave considerable thought to what my organization could do to protect the recipients of our blood products. I accumulated what literature existed at the time which was available to other blood banks and commonly used, and upon return to my facility, I initiated a conference within my organization in order to arrive at an action decision.
After discussions with my medical director and staff, all of whom had reviewed what documentation was

available, it was an unanimous decision that some action must be taken to reduce the chance of our blood products transmitting AIDS. It was common knowledge within the medical community that the majority of AIDS cases were male, homosexuals, and we should attempt, through a variety of techniques, to eliminate from our donor pool any people whose lifestyle had shown a high incidence of AIDS or hepatitis B. Published data had demonstrated that the major risk group for AIDS (i.e. male homosexuals) also had a very high incidence of a history of hepatitis B. This had been demonstrated by numerous surveys over the previous 3-5 years which had been published in the public health literature.

9. My staff and I considered it prudent to act immediately since inaction while awaiting the completion of long-term studies could be hazardous or lethal to the recepients of our blood products. Even though more selective or additional donor standards might result in the rejection of an unknown number of otherwise safe donors, a more responsible and prudent philosophy was felt necessary to protect the recipients of our products. Hence, my organization established a new Informed Consent specifically requiring donors to state their sexual perference since male homosexuals were considered the major risk group. A policy was established that the personnel responsible for screening

our donors would ask direct and penetrating questions as to sexual perference and furthermore, the donors would be asked to attest to the accuracy of their answers by signature. In addition, we instituted a "hands on" examination for lymphadentopathy (i.e. swollen lymph nodes) bilaterally at five sites of the body since the earliest clinical sign of AIDS infection was commonly known to be swollen lymph nodes. In fact, the earliest name given to the hypothesized virus thought to cause AIDS was the lymphadenopathy associated virus (LAV). Although we anticipated an unknown percentage of otherwise healthy donors would be excluded on this basis, we felt it prudent to be "on the safe side" and were willing to work harder at recruiting more and new donors to replace those excluded. Subsequently, we found less than 5 percent of any of our otherwise healthy, qualified donors demonstrated transitory, swollen lymph nodes. In addition, we also introduced a laboratory, surrogate test based upon the November 1982 data presented by Dr. Evatt. Upon examination of his data, it was our conclusion that three surrogate tests could eliminate at least 2/3rds of the potentially infectious donor population. We decided to measure for lymphopenia (i.e., abnormally low lymphocyte levels) as our surrogate test. We did not perform the T-4/T-8 surrogate test due to the exceptionally high capital costs to our small organization. Similarly the costs of

performing the hepatitis B, anti-core test were somewhat higher than the cost for performing ~~lymphatic~~ lymphocyte counts. Our experience since full implementation of this policy in January/February of 1983, has demonstrated a high degree of success in that none of our products have been associated with the transmission of either AIDS or hepatitis.

10. In January of 1983, I participated in policy making as a member of the Executive Committee of ABRA resulting in a recommendation to this membership that they intensify their donor screening through donor education; the use of a stronger Informed Consent; a more intense, confrontation-type medical interview of the potential donors; the requirement that the donors acknowledge by signature they are not members of the risk groups; and additional questions to elicit any signs or symptoms associated with AIDS.

By 1984, blood which was not tested by one of the following three tests: T4/T8 cell test, lymphocyte count or hepatitis B core-antibody was unreasonably dangerous. A reasonable blood bank would have at the very least performed one of the above tests. To not test blood by any of the above three tests was unreasonable and negligent. Any blood bank which did not employ one of the three above tests was negligent. Not performing one of the above three tests was the cause of plaintiff receiving the HIV virus from the

transfusion.

These tests do not create undue expenses as can be seen by a comparison of my own organization's charges for our major product, plateletpheresis-derived platelet concentrates, and that of the Bergen Community Regional Blood Center, ~~shows that~~ during the period of 1983 and 1984, according to the fee schedule of the Bergen Community Regional Blood Center effective March 1. 1984 which I have in my possesion and have examined, ~~shows~~ their price was $425. My price was $365.00 for each plateletpheresis-derived pack. We paid our donors $50.00 to $75.00 for their time and effort, and the Bergen Community Blood Center give no cash payment to their donors. Thus, the discrepancy between our two fees is greater than the fee schedules would indicate. Hence, The failure to test was a lack of reasonable quality control, and created an unnecessary risk to plaintiff. The alternative to testing, i.e. AIDS infection and death, far outweighs the additional cost of testing and increased recruiting costs.

I certify that all of the above statements made by me are true and that if any of the above statements made by me are willfully false I am subject to punishment.

Thomas M. Asher 3-29-90

Thomas M. Asher, Ph.D. Date

Mr. DINGELL. What would your comments be, gentlemen of the panel, with regard to the last-read statement or the earlier statement from Dr. Asher?

Mr. Eckert?

Mr. ECKERT. I agree.

Mr. DINGELL. Dr. Ratnoff?

Mr. RATNOFF. I think that's reasonable.

Mr. DINGELL. It's a fair statement and you agree?

Mr. RATNOFF. One has always to put one's mind back to 1984 though—1983—and what seems clear now may not have seemed so clear then.

Mr. BROWNSTEIN. Indeed, those are the data that Dr. Evart had presented to our medical and scientific advisory council which were reviewed and supported in January of 1983.

Mr. DINGELL. Thank you.

Mr. CONANT. In defense of hindsight from San Francisco as well as Los Angeles, the—we were publicly at the University calling on the blood industry to introduce surrogate testing in February of 1983.

Mr. DINGELL. I think your record is a good one and a clear one, and I don't think you need to be sensitive about it, Doctor.

Mr. CONANT. I was joined by the then Dean of the University of California Medical School at San Francisco and a number of other AIDS experts, so it wasn't just me. It was a number of experts, acknowledged experts in the field, experts in both AIDS and Hepatitis B calling for this testing.

Mr. DINGELL. Thank you. Mr. Brownstein?

Mr. BROWNSTEIN. Yes, I would like to just add for the record that, indeed, those data were presented in January of 1983 and they were reviewed and supported by our MASAC, but supported that, if verified. Our medical body thought there was more analysis that was needed, because that was the first time we had seen such data.

Mr. DINGELL. Thank you. The Chair notes that the time of the Chair has expired. The Chair recognizes the gentleman from North Carolina, Mr. McMillan.

Mr. MCMILLAN. Thank you, Mr. Chairman. Gentleman, we've used the word, "consumers," on a number of occasions. What do we mean by "consumers" in this particular situation? Anyone?

Mr. ENGLEMAN. The main consumer is the patient who uses blood.

Mr. MCMILLAN. But the patient doesn't really make a decision about where the supply comes from and how it's been screened and tested.

Mr. ENGLEMAN. Well, it's actually quite extraordinary that it is the patient and the public in general that has brought the pressure to bear on the industry to make the kinds of fundamental changes that we've witnesses over the past few years.

Mr. MCMILLAN. Well, I'm really thinking ahead in terms of exercising discipline. It seems to me the consumer has an intermediary and that is the physician or the hospital that's responsible for the use of the product. Is there enough input from that perspective in terms of decisions that should have been made in the past or ways we should approach addressing this in the future?

Mr. CONANT. Mr. McMillan, certainly if we look back, there was not enough input from physicians and in the documents that I have reviewed, both from California and from other States on the West Coast, physicians were being constantly reassured by the blood industry that the blood was safe and that the blood industry was, in fact, educating donors and getting high risk donors to self-defer.

Doctors were told over and over again that the chance of getting AIDS is one in a million. I think that, had physicians seen the escalating number of transfusion associated AIDS cases published, if they had seen the information being given to donors when they went in, if they had seen the lack of extent of educational programs, physicians would have brought pressure on the blood banking industry to do more.

Let me give you a simple example. Again, as a practicing doctor, I can tell you that people engage in a lot of denial. They don't want to believe they're at risk for some terrible thing like AIDS. The information for IV drug users that the blood industry generally used, stated something like, have you ever abused IV drugs?

Well, I can tell you that most people who shoot drugs don't think they abuse them at all. They use them just right so they don't hurt themselves. So, any practicing doctor would have told them that that's a terrible history. What you've got to say is; have you ever shot a drug into your vein?

Only if you are explicit, will you eliminate the chance for denial and truly educate the donor. I don't think the doctors or the hospitals knew what the blood industry was really doing in the time period from 1983 to 1985.

Mr. MCMILLAN. I appreciate your candid answer on that. I think that maybe the blood industry is partly to blame for that, but I think perhaps it's much broader, it would seem to me. There's a lot of education that hasn't been transmitted with respect to AIDS that perhaps still exists out there among professionals who the public should expect should know better.

It comes up in the course of debates on a whole range of issues around this Congress, not just specifically this. Your candor is, I think, important, and we need more of that.

Mr. ENGLEMAN. It is interesting to note that this is one of the few examples where we had a disease about which the public was at least as well educated as many physicians were. In addition, in response to this, I think that in the State of California, a law was passed in the last year called the Gann Act. It ensures that physicians inform their patients of the alternatives for transfusion that they might face at the time of surgery.

I believe this is unique to California, but perhaps it's a law that should be considered for the rest of the country as well.

Mr. MCMILLAN. I have a few more technical questions. How much time have I got?

Mr. DINGELL. The time of the gentleman has expired.

Mr. MCMILLAN. Thank you.

Mr. DINGELL. Mr. Brownstein, you had a comment you wanted to make and I think Dr. Ratnoff. Gentlemen, you and other members of the panel who want to comment on the last points raise should feel free to do so.

Mr. RATNOFF. I just wanted to comment on the term, "consumer," and its implications. The implication is that the consumer perhaps should be in a position to exert more influence and no one will quarrel with that.

As I pointed out in my introductory remarks, here the consumer, my patients, the hemophiliac, in fact, refused to recognize the dangers presented to them by the use of material that could be and, in fact, probably was contaminated with the AIDS virus. I regret to state that the Hemophilia Foundation backed him up because their early recommendations were for the hemophiliacs not to change what they were doing, not to stop using contaminated materials.

They made an exception for this, that if you had a patient who had never been treated before, then use the individual donor cryoprecipitates. I think that one must be very wary before one asks an uneducated-in-that-regard group to make a therapeutic decision. We see this now unfortunately en masse in the patients with AIDS who don't happen to have hemophilia, the great bulk of patients.

Mr. BROWNSTEIN. I would like to comment on that, but before I do, I would just like to comment with respect to the role of the consumer. I think that the consumer is a little bit removed. The consumer does not wake up in the morning and say, I'm going to purchase a blood donation today.

I think that Dr. Eckert's point about making that—in franchising consumers who are heavy users of blood products, is a very good one, with a vote on the Blood Products Advisory Committee of the FDA. I think that that is an excellent place where the consumer can have a voice, particularly such as people with hemophilia, sickle cell anemia and thalossemia.

In response to Dr. Ratnoff's comment, the way in which the National Hemophilia Foundation is structured is that we have a prestigious panel called the Medical and Scientific Advisory Council which I made reference to before. They deliberated over the scientific data, including the presentations that were made by Dr. Evatt to the Medical and Scientific Advisory Council.

Since Dr. Ratnoff is so highly regarded by the hemophilia community, his views were certainly well known to the members of this medical body that met in January of 1983. Indeed, part of his recommendations were incorporated into the recommendations of the National Hemophilia Foundation, and part were not.

The position that was represented was that of medical clinicians and scientists, not the consumers, although there were two consumers who were present. Also, the way we have our organization structured, ultimately, any position of our medical leadership needs to be eventually ratified by the consumer leadership.

It's important to remember at that time that AIDS was truly an Andromeda Strain. No one knew what it was. We did not know it was a virus and we—I guess we referred to it as the AIDS agent. This was well before—years before Dr. Gallo identified what was then called HTLV-3 in his laboratory.

With respect to the data that Dr. Ratnoff made reference to earlier concerning the difference between the use of cryoprecipitate and Factor VIII concentrates, the National Heart, Lung and Blood Institute funded transfusion safety study, does indeed look at the data from different parts of the country and there is one place in

the United States where the use of cryoprecipitate is the dominant mode of treatment and that is in Seattle, Washington, through the excellent care that's provided through the Puget Sound Blood Center.

The data there reflects that about—that over 35 percent—and this is from the best of my recollection, but I'll be able to provide you more details on this data—greater than 35 percent of the people who used cryoprecipitate there are HIV positive in contrast with the data I shared with you earlier that 50 percent of the overall hemophilia population, largely overwhelmingly dependent upon Factor VIII, were infected.

However, just consider that the clotting factor, the thousands, the pooled clotting factor, the thousands of donations, are harvested from throughout the United States and centrally manufactured, whereas the cryoprecipitate is local, single donor source material. Just imagine in some of the higher risk cities, other than Seattle, the higher risk areas that were identified earlier on—New York, San Francisco, for example—people with hemophilia, adults with hemophilia, are subject to 600 to 800 units of cryo during the course of a year, and that is, of course, if they have severe hemophilia.

Clearly the amount would have been much higher in these cities. Eventually, what we have found is that continued cryoprecipitate use equals the same amount of exposure as with the use of clotting factor concentrates, as is the case with the transmission of hepatitis through the clotting factor and cryoprecipitate. The difference is a matter of time.

The young children who use, let's say, only 50 units of cryoprecipitate as opposed to the adults who might use 6-800—and I'm talking about those with severe hemophilia—the young children we might buy time for by putting off the exposure. The real difference is really the amount of units of exposure, rather than cryoprecipitates or clotting factor.

Further, as Dr. Ratnoff mentioned before, we now have wonderful methods of inactivating the virus in the clotting factor concentrates, and these methods have proven to be quite successful. Now, the clotting factor is quite safe. Thank god, through the studies that we are doing at the National Hemophilia Foundation, there are no further seroconversions with people using these new products.

I see that gavel, Mr. Chairman, so I will sum up.

I think I have made my point that basically we see that there is very little difference in the cryoprecipitate and the clotting factor.

Thank you.

Mr. DINGELL. The Chair recognizes now the distinguished gentleman from Georgia, Dr. Rowland.

Mr. ROWLAND. Thank you, Mr. Chairman.

For the record, would you define surrogate testing for me, someone?

Mr. ENGLEMAN. In the case of AIDS, Dr. Rowland, the surrogate tests were tests for the presence of finding an abnormality that was common in individuals felt to be at high risk for AIDS—homosexual men, for example; IV drug users, for example—but uncommon

in the general population, particularly uncommon in the general population of blood donors.

Mr. ROWLAND. Specifically, could you name a test for me?

Mr. ENGLEMAN. The T-cell test that we used, for example.

Mr. ROWLAND. The Anti-B Core test in Hepatitis B is a surrogate test.

Mr. ENGLEMAN. The antibody to Hepatitis B Core would be a surrogate test for non-A non-B Hepatitis or HIV, yes.

Mr. ROWLAND. Right. OK. Thank you. I just wanted to get that on the record.

We have already been over this. But let me go over it just briefly again.

A meeting with CDC in January of 1983, a report, where there was opposition to this surrogate testing by representatives of the blood banking industry because of the cost and because of the fact that they thought they might lose donors, rather than basing this on scientific principles, would you all believe that that took place?

Mr. CONANT. The last part of your question, sir?

Mr. ROWLAND. Rather than basing it on scientific principle, they based their reasons for not further exploring this on loss on donors or the cost.

Mr. CONANT. Right. We are told that they were concerned about supply rather than safety, and that it was cost and loss of donors that was the primary concern.

Mr. ROWLAND. If all collecting points did the same kind of tests, that would sort of neutralize itself out, I guess. And really, the costs would be even across the board, essentially.

I guess the thing that they looked at more was the loss of donors, was the thing that they really feared more than anything else.

Mr. Chairman, I want to place on the record Exhibit C, a report to the Board of the Committee on Transfusion-Transmitted Diseases. It was dated January 24, 1983, by Dr. Joseph Bove of the American Association of Blood Banks. Maybe we can put that in the record. [See p. 73].

Mr. DINGELL. Without objection, so ordered.

Mr. ROWLAND. OK. As I understand, the Red Cross, the AABB and the Council of Community Blood Centers between them probably collect about 98 percent of the blood in the country.

Let me read a statement from that, if I may. Dr. Bove seems to be more candid in this report. In the second paragraph, for example, he reports a new case of an infant in Texas who contracted AIDS after transfusion from a donor who had AIDS, concluding this case increases the probability that AIDS may be spread by blood.

Dr. Bove continues by noting that the CDC may even have a few more transfusion AIDS cases, stating that, and I quote: "The most we can do in this case is buy time. There is little doubt in my mind that additional transfusion related cases and additional cases in patients with hemophilia will surface."

But Dr. Bove then added this warning: "...we do not want anything that we do now to be interpreted by society (or by legal authorities) as agreeing with the concept—as yet unproven—that AIDS can be spread by blood."

There is pretty plain language here. It seems to be that AIDS is probably spread by transfusion, in most cases it is virtually certain, in more cases it is virtually certain, but maybe we do not want to really acknowledge that now at this time.

Do you agree with that, based on these statements from this report?

Mr. CONANT. Like you, Dr. Rowland, I am trained as a physician, not a lawyer. And I do not know what some of these words, like "conspiracy" mean. But I went to a meeting the month after that memo that you just read was issued, where Dr. Bove spoke to us publicly as physicians at NYU, and told us that he had serious reservations about even the fact that there was transfusion-associated AIDS. And so he publicly was reassuring us that the blood banks were doing all that they needed to and that he doubted that there was transfusion-associated AIDS. And that speech was published.

And yet we now have this memo where, as you say, he is pointing out that I believe that the best we can do is buy time, that he doesn't want anything that they do to be construed by society or lawyers as agreeing with the concept. And then on Page 2 he says: "I hope that we are equipped psychologically to continue to act together." He has been in contact with Dr. Katz and Dr. Menitove, and believes the three of us can act together to "work out whatever new problems may arise." That sounds like collusion. I just, I do not understand it.

Mr. ROWLAND. I was going to read that, but you have already read it for me, so I——

Mr. CONANT. Sorry about that.

Mr. ROWLAND.—appreciate that.

Well, I see my time has expired, Mr. Chairman. So Thank you very much.

Mr. DINGELL. The time of the gentleman has expired. The gentleman from Ohio, Mr. Oxley.

Mr. OXLEY. Thank you, Mr. Chairman.

Dr. Engleman, persons in the blood banking community who advocated surrogate testing to ascertain certain groups at high risk for AIDS were apparently subjected to strong pressure from blood collectors, including the Red Cross, as well as criticism from their peers.

I think you are aware of an affidavit that the committee has received from a Dr. David DeJongh. I ask that it be placed into the record as Exhibit E.

Mr. DINGELL. Without objection, so ordered.

[The document follows:]

EXHIBIT E

IN THE SUPERIOR COURT FOR THE DISTRICT OF COLUMBIA
Civil Division

CYNTHIA D. OKORO, Plaintiff	)	
v.	)	Civil Action No. 5325-87 (Civil I - Judge Salzman)
THE AMERICAN RED CROSS (D.C. Chapter) Defendant	)	

AFFIDAVIT OF DR. DEJONGH

I hereby swear and affirm that the following is a true and accurate statement of the facts contained therein:

1. I am Dr. David DeJongh, and in 1983 and until September, 1984, I was the Director of the Blood Bank at Charity Hospital in New Orleans, Louisiana. Our blood bank was both a collection facility and a transfusion service for both Louisiana State University School of Medicine at New Orleans and Tulane University School of Medicine teaching facilities.

2. During the time that I was there, we had strenuously recommended that safety required that the Hepatitis B Core Antibody test should be routinely utilized by all blood collection facilities, including our own.

3. This testing was recommended in order to detect past-infection by Hepatitis B virus that might not be identified by the surface antigen test.

4. Additionally, at this time it was widely known that

routine screening for Core antibody (anti HBc) would reduce the risk for both Hepatitis B virus (HBV) and Non-A/Non-B (NANB) Hepatitis.

5. Our recommendation was further supported by the knowledge that AIDS occurs among populations that are sources of HBV-positive plasma.

6. We were unable to institute the test at our hospital because the committees that were designed to make these determinations felt pressure, particularly from the blood industry, including the American Red Cross. The pressure that was asserted was designed to keep blood banks from straying from the course set by the blood industry, including the Red Cross, that course being to avoid the use of the Core Antibody test.

7. The opposition by the blood banking industry and the Red Cross was due to their concerns about the cost of the tests, the potential loss of 4-6% of the blood collected, and their fear that the institution of the Core test by some blood banks would create a standard of care by which other blood banks would be required to abide.

8. My knowledge regarding these facts is based on my memory of having spoken to various individuals who had informed me that it was pressure from the blood industry and the Red Cross for them not to stray from the course set by the blood industry and the Red Cross that was a major factor in the various committees' decisions not to pursue additional testing.

I hereby affirm under penalty of perjury that the foregoing is true and complete to the best of my knowledge and recollection.

David DeJongh, M.D.

Subscribed and sworn to before me this 2nd day of November, 1989.

Notary Public

My Commission Expires:

NOTARY PUBLIC STATE OF FLORIDA
MY COMMISSION EXP. APR.22 1993
BONDED THRU GENERAL INS. UND.

0042

Mr. OXLEY. Do you have a copy of that affidavit, Doctor? While you are looking for it, I will continue.

According to this sworn affidavit, Dr. DeJongh and others at the Charity Hospital Blood Bank in New Orleans advocated the Hepatitis B Core Antibody test to reduce the risk of non-A, non-B Hepatitis as well as transfusion of AIDS.

However, as stated in Paragraph 6, and I direct your attention to Paragraph 6, Doctor, he states in that deposition, quote: "We were unable to institute the test at our hospital because the committees that were designed to make these determination felt pressure, particularly from the blood industry including the American Red Cross. The pressure that was asserted was designed to keep blood banks from straying from the course set by the blood industry, including the Red Cross, that course being to avoid the use of the Core Antibody Test."

Now, Dr. Engleman, when your blood center began using a surrogate test, in this case, a T-cell ratio test, were you subjected to such criticism or complaints?

Mr. ENGLEMAN. Yes, we were. And quite honestly, we were very surprised. We did not necessarily expect the rest of the industry to immediately take up this test that we were using. On the other hand, we did not expect the negative reaction that transpired.

Mr. OXLEY. Could you be a little more explicit? How did that negative reaction take place?

Mr. ENGLEMAN. Well, we spent some considerable effort encouraging blood bankers to look at our test and either adopt it or subsequently adopt the Hepatitis B Core Antibody test. And statements made in the press at that time suggested, among other things, that we were undertaking our testing as a publicity stunt, that we were creating unnecessary panic and anxiety, that AIDS really wasn't the problem that we thought it was with the blood supply, that perhaps we were making some secret profit from doing our testing.

None of these things were true. It is my belief that at least part of that negative response reflected a concern that everybody hang together and that a consensus be reached and that we all behave the same way.

In our judgment, this is part of the problem, the problem of discouraging innovations or differing ideas, so that everyone acts in unison. That can be a strength in some circumstances. In this case, I think it contributed to the tragedy.

Mr. OXLEY. In fairness to those folks, Doctor, you were talking now about the early 1980's.

Mr. ENGLEMAN. Yes.

Mr. OXLEY. So in some way, those of us on the committee as well as those testifying are somewhat using hindsight in the kind of a context of "we told you so" and "here's what happened." My guess is that most of those people were acting in what they considered to be good faith, based on the knowledge that they had. Is that a fair assessment?

Mr. ENGLEMAN. Well you may have disagreement on the panel, but in my view, they were acting in good faith and they were doing the best they could, but they were blinded. They did not objectively analyze the data that was available. The notion, for example, that the risk of contracting AIDS from a blood transfusion was less than

1 in a million, as you've heard repeatedly here, was absurd, was absurd at the time it was suggested, but it was never corrected. It was allowed to continue and fester in the public mind for 2 years thereafter. But I do believe that they were acting with the best of motives.

Mr. OXLEY. I see Dr. Conant chomping at the bit down here, so I'll give him a chance to respond.

Mr. CONANT. Thank you. Without trying to impugn the motives of the blood industry, I would disagree with your characterization that it was before the AIDS epidemic was well recognized. I would remind you, sir——

Mr. OXLEY. Either in the medical community or the public?

Mr. CONANT. And the general public. For example, when IV drug users were being reported with AIDS in August and September of 1982, that's 6 months before the time that we're discussing here, Time, Newsweek, all of the periodicals, ran feature stories often with pictures of AIDS patients on the covers of the magazine discussion the epidemic, pointing out the IV drug users were getting the disease and it looked like it might be transmitted like hepatitis B and even suggesting that it raised the concern that it might be in the blood. That was 4 or 5 months before the first case of transfusion associated AIDS was even recognized.

And so it's not correct to characterize the epidemic as being unknown or unrecognized at that point. It had been named AIDS by May of 1982, we had already had 900 cases of AIDS in the United States by the time the first transfusion associated AIDS occurred and the disease was well recognized by that time.

Mr. OXLEY. Dr. Conant—I'm sorry, Mr. Eckert.

Mr. ECKERT. Mr. Oxley, could I just add that I wasn't present at the January 1983 meeting that CDC called in Atlanta, and I haven't read a transcript of it. I don't know if a transcript exists, but I have read reports of it, quite a few reports. And they way I would characterize that meeting was a public warning by CDC, which is the government's expert Agency on epidemiology. These are the people who supposedly know most about epidemiology. And it was a bold thing to do to issue a public warning.

And we hear in the press and in Congress and everywhere else a lot of criticism of government agencies that don't do their job right, but it seems to me that they ought to get credit when they do do their job right, and it seems to me that CDC did its job. It issued a public warning. The Public Health Service, then, in the document that I cite on page 3 of my prepared statement, by March 4, 1983, the Public Health Service interagency group had concluded that "the available data suggest that AIDS is caused by a transmissible agent" and "the likelihood of blood transmission." That was an MMWR of March 4, 1983.

So, by that juncture, the hypothesis, which was the reigning dominant hypothesis, that AIDS was caused by a blood borne infectious agent was unmistakable, absolutely unmistakable. I was in at the events that Dr. Conant has characterized in 1982, but these events of early 1983, to me, are unambiguous and CDC did its job.

Mr. OXLEY. So your argument is that you don't think they were acting in good faith. You don't agree with Dr. Engleman?

Mr. ECKERT. I think they ignored a warning. Good faith is almost a lawyer-like term. I don't know quite how to characterize that, but they ignored a warning. They chose to ignore a warning. This was a public warning and they decided to take a different course of action.

Mr. OXLEY. Dr. Conant, let me ask if you're familiar with the situation in San Jose, California where the American Red Cross determined that it would be best to test for the Anti-B core and then the decision was later reversed. Are you familiar with that situation?

Mr. CONANT. No, sir.

Mr. OXLEY. Dr. Engleman, are you?

Mr. ENGLEMAN. It's my understanding that the Red Cross in San Jose actually did decide to adopt to surrogate testing in 1984 and instituted the hepatitis B core antibody test. What is regrettable is that the rest of the Red Cross around the country, including those high risk areas around the country, Los Angeles, New York, parts of Texas, et cetera, chose not to, and the Red Cross as a whole chose not to institute core antibody testing, but I just want to emphasize that San Jose did so. San Jose is not a high risk area. It's located some 50 miles away from San Francisco, and for those of you that aren't familiar with that area, it really does not constitute a high risk area for AIDS, and yet they had the foresight, if you will, to begin surrogate testing. It would have been nice if they'd begun a year earlier, but at least they did begin in 1984.

Mr. OXLEY. Dr. Conant, can you describe the events through which the University of California at San Francisco faculty forced the Irwin Memorial blood bank in San Francisco to adopt the Anti-B core test, in 1983, I believe?

Mr. CONANT. I'll tell you what the events were, but I'm not sure we forced them to do it. Following the CDC meeting where no consensus could be reached by the blood industry as to what should be done, and yet where from our perspective the CDC was urging the blood industry to use surrogate testing by showing them how effective it was on slides and in presented data, I invited Dr. Perkins, the head of the blood bank in San Francisco, to meet with us at our AIDS clinic in San Francisco and discuss what the blood bank was going to do. He reassured us that they were going to screen out through questioning high risk donors that presented at the blood bank, but that they had no plans to institute surrogate testing.

We urged him to institute surrogate testing, because as physicians, we knew that there were people in San Francisco who were engaging in high risk behavior, such as homosexual activity or drug uses, who wouldn't admit even to themselves that that's what they were doing. And that we saw that educational efforts would also fail and that you had to have a back-up screen such as a surrogate test of the product once you had collected it.

When it became obvious that Irwin Memorial blood bank was not going to act on that recommendation, a group of us, including Dr. Paul Volberding, who now runs the AIDS program at San Francisco General, Rudy Schmidt, who was the Dean, Dr. Altman, who is an internationally recognized authority on hepatitis B, and I and some others drafted an open memo to the San Francisco Chronicle

publicly asking Irwin Memorial to look at surrogate testing to try to eliminate AIDS from the blood supply.

Unfortunately, they didn't do that at that time. They only did it in May of 1984. The time that I just referred to was February of 1983. It took them a little over a year to institute surrogate testing, and we were told at the time that the reason they were doing was not because they thought it be effective for AIDS screening, as events have shown that it would have, but in response to what Dr. Engleman was doing down the peninsula at Stanford, because patients getting injured in San Francisco were going to Stanford for their surgery rather than having it in San Francisco because the patients knew that we had an AIDS epidemic and that it was being transmitted in blood.

Mr. OXLEY. Thank you, Doctor. Thank you, Mr. Chairman.

Mr. DINGELL. The Chair would like to sort of complete the record with the very fine list of questions raised by the gentleman from Ohio. Dr. Engleman, I'd like you to refer to San Jose. There was a decision made by the blood bank there to not require further tests. Well, there were two decisions made. One was to require additional tests and then one was not to require additional tests, and I wanted you to comment on that event. They originally decided they were going to have additional tests. They came to the conclusion they would not. Subsequently, they did not. Can you tell us whether the American Red Cross had any part in the change of decisions there?

Mr. ENGLEMAN. Well it's my understanding that, in fact, San Jose Red Cross did institute the surrogate testing. I suspect they did so over the loud protests of the National Red Cross, but I would ask and suggest that you ask the Red Cross about that. How is it that one of their blood banks in a non-high risk area instituted surrogate testing when the remainder of the blood banks, particularly those in high risk areas, did not. But it is my understanding that the San Jose Red Cross did institute the hepatitis B core antibody test as a surrogate test for AIDS in 1984.

Mr. DINGELL. I see. And was there pressure placed on them in connection with that decision one way or the other by the American Red Cross?

Mr. ENGLEMAN. I don't have first-hand knowledge of that, but I would be surprised if there weren't pressure.

Mr. DINGELL. Very well, thank you. The Chair is going to recognize counsel.

Mr. SIMS. Thank you, Mr. Chairman. I wanted to clarify one point here. Dr. Engleman, when your blood bank started this T-4/T-8 test, did you, in fact, identify any donors who were excluded as a result of that test that had donated blood at other Bay Area blood centers?

Mr. ENGLEMAN. Absolutely. We started our screening test on July 1, 1983. Within a matter of a few weeks, we had already identified individuals among the individuals who had abnormal T-cell tests were those who should not have been donating in the first place. Members of high risk groups for AIDS, specifically, homosexual men, who when asked why did they donate blood when they knew, didn't they read the information that they weren't supposed to, they said, yes, but for whatever reason they didn't think they were in that category of risk.

Now some months later, in the Winter of 1984, I believe it was February or so, I received a phone call from a physician elsewhere in California who was very upset because one of his patients who had AIDS, and in fact, was dying from AIDS had told him that he donated at several blood banks, including our own, and was concerned now about the possibility that he had transmitted AIDS. As it turned out, that particular donor had donated at Stanford, but his T-cell test was abnormal and his blood was thrown out and not used. On the other hand, the same individual had donated at other blood banks and his blood was, in fact, used.

Mr. SIMS. He had donated at approximately 12 blood banks, is that correct?

Mr. ENGLEMAN. At least 12 or so donations. I don't know whether they were 12 different blood banks, but they were several different blood banks, yes.

Mr. SIMS. And Stanford was the only one that rejected the blood?

Mr. ENGLEMAN. That's my understanding, yes.

Mr. DINGELL. Why did Stanford reject the blood in that instance?

Mr. ENGLEMAN. We rejected it on the basis of we were using a surrogate test for AIDS and that individual tested abnormal on that particular surrogate test, and on that basis we rejected his blood.

Mr. SIMS. Was one of the blood banks at which this donor gave blood, the San Jose Blood Bank?

Mr. ENGLEMAN. I believe so, yes.

Mr. SIMS. Was that part of the reason why the San Jose Blood Bank decided that they had better have a surrogate test?

Mr. ENGLEMAN. Well, I would, if I had been in their shoes, that would have been a good reason. As good as any.

Mr. SIMS. Thank you, Mr. Chairman.

Mr. DINGELL. The gentleman from Oregon, Mr. Wyden.

Mr. WYDEN. Thank you.

Gentlemen, I think what concerns me the most at this point, is that we have discussed a number of questionable practices that took place in the middle-1980's; and the question really is, which ones of these are taking place today? Which ones do we most have to move to, in terms of initiating reforms?

And one area that I want to explore with you is what's known as the "look back issue": The notion that a blood collector ought to test their inventory when a new screening test is implemented to advise a recipient, based on the latest information, as to whether they got contaminated blood.

Now, Professor Eckert, in March of 1985, when the first test for the AIDS antibody became available, blood bankers began testing new donations, but as a general rule, did not screen the blood on their shelves; is that correct?

Mr. ECKERT. I believe that's correct, as a general rule, Mr. Wyden.

Mr. WYDEN. Would a look back program at that time, have likely prevented the transfusion of some AIDS-contaminated blood?

Mr. ECKERT. Mr. Wyden, if I could elaborate just a bit.

The question that you raised contains really two issues: One is this business of whether the blood banks, when they receive their early test kits, shortly after the test was licensed by the FDA,

should have tested inventory already on the shelves—previously donated units already on the shelves, as well as inventory shipped, I presume, shipped out to blood banks that had not been tested, all before routine testing of new donations began.

That's one issue. I don't believe most blood banks did that.

The other issue you've raised is this issue of look back, which is when a person who comes into a blood bank and is identified by the test for antibody to HIV as being positive; the blood bank then looks back through its previous record of donations for that person and contacts the hospital to whom—to which those—that unit or those units of blood or components were shipped.

I think a look back is a very important matter; because, after all, we are dealing here with an infectious disease which could be spread, not only from the transfusion recipient, but to—to others and to members of the family.

The Presidential Commission on the HIV Epidemic, cited that as an extremely urgent and important matter and I agree.

Mr. WYDEN. Wouldn't it be fair to say then, Mr. Eckert and panel members as well that, at best, our policies with respect to looking back, are uneven.

I note, for example, when the blood industry instituted a test for hepatitis C earlier this year, Professor Eckert, you were one who argued that there should be a look back in that case, as I understand it; and it wasn't done.

Mr. ECKERT. I did, Mr. Wyden, and I argued it very strongly. I was absolutely startled by the—the—what appeared to be a consensus reached in various—not only among the blood banking organizations, but in a—I believe a working group in the various health agencies, that included FDA and NIH and whatever had met and had recommended that we not look back for hepatitis C.

That seemed to me to be a very startling development in the following sense: That they were relying on physicians to contact patients, rather than letting blood banks notify hospitals each time a donor who was—who tested positive for this test came in.

Many patients don't know they have been transfused.

Mr. WYDEN. I think what concerns me the most is that if you look again to the middle-1980's, you see how the look back policy might have made a difference. You describe just—even those few months, as the AIDS' tests were coming online; and yet here we are right at the present period, where we still do not have clear, uniform look back policies to strengthen our blood supply; isn't that correct, Dr. Conant?

Mr. CONANT. To illustrate your case, sir; I know of a situation in the State of Colorado, where the test kits became available. The unit of blood was already collected and was not tested; it went out to a hospital and was not used, returned to the blood bank, was still not tested; went out to the hospital and was transfused into a young mother, who is today dying of aids.

So, it not only is hypothetical, it did occur.

Mr. WYDEN. Dr. Engleman, did you want to add anything on that point?

Mr. ENGLEMAN. Well, again, I want to reiterate Dr. Eckert's comments, that we are dealing with two issues:

One is the testing of blood in storage, if you will, in inventory after a test becomes available, rather than just using the test to test new blood as it—as donors donate. In my view, there is no excuse for not seeking to test blood that has not yet been transfused, just because it is in inventory.

The issue of look back refers, as you correctly pointed out to incidences where an individual comes in to donate blood and tests positive on a test; and you go back or you look back to recipients of this individual's previous donations.

We now do look back for HIV. We do not, or the industry has not yet begun to do look back for hepatitis C. I think there, we could spend hours talking about the difficulties of doing that. In my view, we should be doing hepatitis C look back. But, as I said, it would take a long time to work out all the protests.

Mr. WYDEN. Let me see if I can get one other question in. I know you want to add something, Mr. Eckert, but I think the basic point that I wanted to make, you all have corroborated; which is that some of the problems we saw in the middle-1980's, we are still seeing today—and here is a particular test. I appreciate your clarity on it.

Tell me, if you would—perhaps we will start with you, Mr. Eckert; in terms of the Blood Products Advisory Committee—is this an industry protection program? I mean, they seem to be very resistant to some of the proposals that are being discussed.

Now, I do not profess to know more than what has come out at this hearing today in the documents we have; but how would you characterize that advisory committee?

Mr. ECKERT. That's an awfully strong way to put it, Mr. Wyden.

I would characterize it, I think, the way I—I put it in my prepared statement and my——

Mr. WYDEN. It needs to be opened up.

Mr. ECKERT. It needs to be opened up. In my remarks to the committee this morning—it is a situation whereby the normal processes of the advisory committee process, it winds up getting a lot more information from suppliers than from consumers.

I have emphasized this before. What consumers know about blood—about blood banking and what tests they should argue for and what they should pay for, if they had their choice or right to make such payments, is almost nil.

Consumers do not specialize in this information. They expect the FDA—and they believe—I think probably most American consumers believe that the FDA is making adequate judgments here.

So, we get an advisory committee process that is structured so that the advisory committee and the FDA—the Agency gets a lot more information from one side of the market, if you will, than from the other side. I think that's a very serious deficiency.

Could I add just a brief observation?

Before coming to the committee today, I read the Federal Advisory Committee Act. This is Public Law 92-463, an Act of 1972, as amended; and it appears in, and I am reading from Title V of the U.S. Code, the Appendix, Section 5.

It clearly spells out that standing committees of the House and Senate have—have authority to make sure, as they consider legislation, or as they consider other matters, pertaining to the advisory

committee process, that the information that is generated by this process is, and I quote the statute: "fairly balanced," Section 5(b)2 reads that "they can require the membership of the advisory committee to be fairly balanced, in terms of the points of view represented and the functions to be performed by the advisory committee."

That's where I took my language of "fairly balanced," in my statement. I think it is just very important that something be done to restructure the balance of that advice.

Mr. WYDEN. Those are thoughtful comments.

Let me just ask our panel members. We have a vote.

Do any of you disagree with Professor Eckert's basic view, that the process needs to be opened up or restructured, so as to provide for a larger consumer role and a vehicle for disseminating information? Is there any disagreement among our panel members on that?

[No response.]

Mr. WYDEN. Let the record reflect that there were no verbal answers.

Mr. Chairman, thank you.

Mr. DINGELL. Gentlemen, this thing tells me everything I want to know about what is going on the floor and a good deal more.

Gentlemen, the committee thanks you for your very helpful testimony and your comments.

Mr. Eckert?

Mr. ECKERT. Mr. Chairman, thank you. Could I just make one final remark?

A question that Mr. Wyden asked at the beginning of the question time, the import of which I didn't quite see I think is a very important matter.

He was referring to the number of people estimated by CDC who are still alive, the 12,000 who, as he asked the question, might be blood donors, and as I said in my prepared statement, I think it is very important that we reform blood donor screening practices to remove from the donor pool anyone who has been transfused since 1977, not only for the purpose of not transmitting HIV but for the purpose of transmitting viral hepatitis, which from a public health standpoint, although it is not unambiguously fatal a disease, it is the much larger problem and causes each year I would estimate annual deaths that exceed all the transfusion AIDS cases to date.

So this is the issue that I raise and that you were kind to let me emphasize again here. We need better donor screening practices, not just for those 12,000 folks but for a lot more.

Mr. DINGELL. Gentlemen, I think in view of the fact that this is probably the last question to be directed, would any of you like to, feel that you have anything else you would like to say?

Dr. Engleman, do you have a comment?

Mr. ENGLEMAN. Yes, just briefly, we have made no mention today about the ability of many patients to donate their own blood and use their own blood, so-called autologous blood, which by definition is far and away the safest blood that one can receive since you don't become exposed to any agents that you aren't already exposed to. We have not used in this country nearly as much autologous or one's own blood as is possible and I think we should go on

record as endorsing that concept and doing whatever can be done to make autologous blood available to patients who can benefit from it.

Mr. DINGELL. That is a more expensive way of doing business, though, is it not?

Mr. ENGLEMAN. Not much more. There is an administrative cost of setting aside one's own blood and making sure that it only gets to the individual that donated it but in essence it is really not substantially more expensive and it is a whole lot safer so in the end I suspect that we would be saving money by avoiding medical problems.

Mr. DINGELL. I happen to think it is a very fine idea. I just wanted to be sure that we have that question in the record.

Dr. Conant, do you have a comment, the last comment before we excuse the panel?

Mr. CONANT. I would like to second what Dr. Eckert recommended but I think that future medical historians looking back on this period even today will say that it is astounding that we continue to collect blood from individuals who have not been screened for lifestyle and behavior that may put them at risk for diseases that we have not yet even identified, and of course some of those behaviors may not be socially acceptable, such as promiscuous sexual behavior, so we might not want blood from prostitutes but some of the behavior might be quite socially acceptable. I am not sure we should be taking blood from physicians who stick themselves with needles all the time and are being exposed to a whole variety of agents, so I think that a more detailed exclusion of donors would certainly be the best interest of our patients.

I would like to conclude, Congressman Dingell, by thanking you for having us come and having an opportunity to share with you some of these concerns that many of us have had for a decade.

Mr. DINGELL. Gentlemen? Dr. Ratnoff and Mr. Brownstein?

Mr. RATNOFF. The only comment I would make, Mr. Dingell, aside from appreciating the privilege to talk here, is that I think that one should realize that the blood products industry in terms of those who make clotting factors become highly sensitive to the issue of transmitting disease and that they have made a much greater effort in this direction than perhaps they should have originally and so it isn't all a one-way street.

The effect of AIDS in the hemophiliac population is not to be believed. I have done two separate attacks on this.

One has been to say what's happened to our own hemophiliacs who were transfusing themselves and the answer is about a third of them are now dead with AIDS, and the second thing I have done is to have a study with a local statistician on every patient who ever has crossed our threshold with hemophilia or a hemophiliac relative and there the result is absolutely extraordinary. The life expectancy of the hemophiliac in—let's see if I have got the exact number here—in the beginning of this century the life expectancy was about 40 years. Then with the introduction of ways of treating hemophiliacs with plasma and with fractions of plasma such as I spoke of before, the life expectancy jumped 20 years to 60 years for severe hemophiliacs.

Now we are right back to 40 again.

All the gains we have made have now been lost.

Mr. DINGELL. Mr. Brownstein.

Mr. BROWNSTEIN. Yes, I would like to just close and thank you for holding this meeting.

I think that it is correct that some members of the subcommittee observed that the blood supply has become more safe than it was, say, 8 years ago. I think that the risk that we face now is becoming complacent and not maintaining our vigilance and making sure that the blood supply remains safe.

I would like to close by Mr. Wyden asked if anyone disagreed. I just want to strongly agree with Mr. Wyden because in 1981 and 1982 there was no one representing the hemophiliac community on the Blood Products Advisory Committee and today there is a physician and a non-voting consumer representative and I have directly observed that the hemophiliac community has since become more enfranchised and involved and been able to contribute more to the deliberations that are taking place here as a result of that.

Again, thank you very much for holding this hearing.

Mr. DINGELL. Gentlemen, you will forgive me for hastening from the room because there is another vote on the floor and you have kind of observed we have a curious process of running for votes and then coming back and trying to do our business.

First of all, to each of you our thanks. We greatly appreciate your assistance today. Your testimony has been outstanding and I think everybody enjoys not only the greatest respect for you but also has the deepest gratitude to you for your assistance to us. These matters are going to be pursued responsibly by the committee but I assure you vigorously.

I can also tell you that there will be no one who will be forgetting the lessons of the past or failing to take the steps that need to be taken to assure safety of our blood supply to everybody when these hearings are concluded.

The Chair will adjourn the committee for approximately 20 minutes, during which time the Chair will go to vote.

The Chair announces that immediately following that the second panel will appear and everyone should plan their affairs accordingly.

The subcommittee stands in recess then until 20 minutes after the hour of two o'clock.

[Brief recess.]

[Testimony resumes on p. 125.]

[The following exhibits were submitted:]

EXHIBIT A

CONFIDENTIAL

Summary Report on Workgroup to Identify Opportunities for Prevention of Acquired Immune Deficiency Syndrome
January 4, 1983

I. The Meeting

On January 4, 1983, from 8:30 a.m. to 4:30 p.m., a meeting was held in Atlanta to consider existing opportunities for prevention of Acquired Immune Deficiency Syndrome (AIDS), both by person-to-person transmission and by blood or blood products. This meeting was a follow-up to a meeting held July 27, 1982 in Washington, D.C. which considered the significance of the occurrence of AIDS in three patients with hemophilia.

Invited participants included representatives of the National Hemophilia Foundation, American National Red Cross, various blood banking organizations, National Gay Task Force, New York and San Francisco Health Departments, Conference of State and Territorial Epidemiologists and the Pharmaceutical Manufacturers Association as well as staff members of the CDC, FDA and NIH (Attachment 1).

The morning was devoted to reviewing recent information pertinent to AIDS, risk groups and the blood and plasma donation process: the epidemiology of AIDS, AIDS among persons with hemophilia and those receiving transfusions, potential laboratory screening tests, current recommendations and regulations for screening of blood and plasma donors, the demographics of blood donation and the separation and processing of blood and blood derivatives, including Factor VIII. Discussion was then held on various alternative opportunities for prevention.

II. Aspects of Discussion

A. AIDS continues to be a major public health problem. In addition to the previously described high risk groups (homosexual men, intravenous drug users, recently arrived Haitians, etc.), persons with hemophilia are also at increased risk of developing AIDS presumably by introduction of a transmissible agent in Factor VIII concentrate. Five cases of AIDS have been reported in persons with hemophilia since the three described in July and [illegible] three more are considered to be possible cases.

B. One case of AIDS has occurred in an infant who received a platelet transfusion from a man who subsequently was diagnosed as an AIDS patient. Several other AIDS cases under investigation (five) have no risk factors but have received blood products within the past two years. Some participants were reluctant to accept the hypothesis that AIDS has been transmitted by whole blood in the absence of additional evidence.

C. Guidelines for prevention of AIDS cases by person-to-person transmission were generally accepted by the workgroup (proposed guidelines are in Attachment 2).

D. A consensus was reached that it would be desirable to exclude high risk donors to reduce the risk of AIDS transmission via blood and blood products. However, no consensus was reached as to the best method of doing this. The principal strategies are:

1. voluntary restriction by potential donors within high risk groups;

2. exclusion of donors on the basis of history and/or physical examination at the time of donation, e.g., a positive response to questions such as, "Have you had sexual contact with another man?", "Are you a past or present intravenous drug user?", "Are you Haitian?" etc. On physical exam, patients with lymphadenopathy, etc. could be excluded.

3. Use of a "surrogate" laboratory test; a test which when positive is associated with high risk groups for AIDS.

4. A combination of these strategies.

All these strategies will be difficult to evaluate for effectiveness.

E. Voluntary restriction has the advantage of enabling high risk groups to play a major and responsible role in protecting others in society. It is independent of the blood supply system. It is inexpensive, and is relatively easy to initiate. The disadvantages are that it has the limitation of not being able to influence less responsible persons and being unlikely to reach and motivate some proportion of those for whom it is intended.

F. Questioning donors for their nationality, sexual orientation or personal habits has the advantages of being an easy extension of the screening history already used in blood donation, is inexpensive, can be directed toward high risk groups and causes little disruption in the blood collection and processing routine. It has the disadvantage of being potentially intrusive into personal matters, may be viewed as unethical, might institutionalize a stigma on groups already prone to prejudice and persecution, and may be ineffective in identifying persons in these high risk groups. Concerns about record privacy have been raised. A considerable proportion of practicing homosexual males may not consider themselves high-risk for AIDS and others may be reluctant to disclose their sexual orientation. Similarly, recently emigrated Haitians and drug users may be reluctant to identify themselves. Some commercial plasmapheresis processors are already excluding by history some AIDS high risk groups.

G. Surrogate laboratory tests have the advantages of being objective and can be done on specimens already being drawn for HBsAg. They respect donor privacy and may be most effective in eliminating potential transmitters of AIDS. They have the disadvantage of adding expense to the blood collection process, both through test cost, administrative overhead, and loss of blood units already collected. Further, they may stigmatize as unsatisfactory many "normal" donors for each potential AIDS transmitter that is rejected.

For example, if the presence of hepatitis B core antibody is used as a laboratory surrogate screening test:

1. In CDC's specimen file, 90 percent of known definite AIDS cases are positive for anti-HB_c and would be excluded as blood donors.

2. Approximately five percent of the general population of voluntary donors are positive for anti-HB_c, though this figure may vary by blood center. These results would be determined after collection, and the collected units would have to be destroyed, unless they could be safely and practically processed into other blood products.

3. The costs of the test might add to the cost of processing. The loss of each destroyed unit represents further expense and there might be additional overhead costs. The costs of preventing an unknown number of AIDS cases (and possibly non-A, non-B hepatitis cases) are unknown, but each such case is very costly in direct and indirect costs and the intangible costs of grief and suffering.

4. Concern was expressed over availability of adequate anti-HB_c test materials. However, information suggests that some companies are already planning production of large quantities of anti-HB_c and that demand would provoke an adequate supply.

5. As the epidemiology of AIDS changes, high risk groups may have lower rates of positivity for anti-HB_c.

6. This additional laboratory test will require new training and procedures for many laboratories.

H. Alterations in blood processing could also reduce the risk of AIDS transmission. The FDA expects an improved Factor VIII concentrate to be available within 12 months. This product would be heat treated sufficiently to inactivate hepatitis B virus and presumably eliminate other transmissible agents from the finished product. Although preliminary data on such treated Factor VIII materials suggest that there is little loss in activity, detailed information on increased costs, product availability and likelihood of reducing AIDS risk are not yet available.

III. Conclusions and Recommendations

A. The workgroup participants represented various organizations, governmental agencies and constituent groups concerned with and affected by AIDS and the blood and plasma donation process. They have differing perceptions of:

1. The likelihood that AIDS is caused by a transmissible agent;

2. The risk of AIDS from blood donation (both whole blood and pooled plasma); and

3. The best approach for establishing altered guidelines for blood donation, donor screening or testing and donor restriction.

B. The workgroup meeting was successful in presenting the most recent data on AIDS and blood/blood products and as a forum for differing views to be expressed. This enabled all participants to gain further insight and appreciation of an extraordinarily complex health problem.

C. I recommend that each Public Health Service Agency (CDC, FDA, NIH) provide candidate sets of recommendations for the prevention of AIDS in patients with hemophilia and for the other recipients of blood and blood products to Dr. Jeffrey P. Koplan, Assistant Director for Public Health Practice, CDC. The three agencies should then develop a uniform set of recommendations on AIDS for your office.

EXHIBIT B

Francis 16

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date January 6, 1983

From Donald P. Francis, M.D., D.Sc., Asst. Dir. for Med. Science, DHVE

Subject Opportunities for Eliminating Blood Donors at Risk for Transmitting AIDS

To Jeff Koplan, M.D., Assistant Director, PPE

The January 4th meeting members failed to agree on recommendations for the best means at this time for decreasing the chance of blood/blood product-associated AIDS. I feel there is a strong possibility that some post-transfusion AIDS and much post-factor VIII receipt AIDS will occur in this country in the coming two years. As it is CDC's responsibility to take every opportunity to eliminate AIDS transmission I think CDC should come out with it's own recommendations. This is especially desirous for whole blood as a panic which could follow the discovery of as few as 20 post-transfusion AIDS cases could result in loss of life from subsequent under-utilization of blood. For hemophiliacs I fear it might be too late. If the T-4/T-8 prevalence data collected to date are reflective of pre-AIDS, 1/3 to 1/2 of hemophiliacs might already be exposed. Despite this grim picture among hemophiliacs however, we should do our utmost to prevent further exposure and recommendations for plasma products should also be made.

I think the following recommendations should be promulgated by CDC with hoped for, but not essential, agreement of FDA:

I. Funding. An additional 10 million dollars should be put forth to expand epidemiologic, etiologic, and clinical studies of AIDS.

II. Whole blood and plasma collection. All blood and plasma donors should be deferred if:

1. They are IV drug users (already in place).
2. They are sexually (heterosexual or homosexual) promiscuous (more than an average of 2 different people per month for the previous 2 years).
3. They have had sexual (heterosexual or homosexual) contact with someone who is sexually promiscuous or an IV drug user in the past 2 years.
4. They have lived in Haiti in the past 5 years.
5. They have a serologic test positive for anti-HBc.

There is good evidence that this will eliminate over 3/4 of AIDS-related donors. It will also defer about 5% of U.S. blood donors and add about $5 to each unit of blood and plasma. These seem to be small prices for preventing a serious disease and a potentially dangerous panic.

III. Factor VIII use.
Only small pool (less than 100 donors) concentrate or cryoprecipitate be used on hemophiliacs starting immediately (after supplies become available). This recommendation should stand until either: 1) knowledge of AIDS permits more accurate recommendations or 2) plasma becomes available which has been collected using the previously stated donor deferral.

I understand that these recommendations will be controversial and that there will be objections by industry and blood bankers. I think we should get comments from these groups and should keep them informed of our to-be-published recommendations. However, to wait for their approval of our recommendations will only endanger the public's health.

cc: Dr. Dowdle
Dr. Curran
Dr. Maynard

EXHIBIT D

Anti-HBc as a nonspecific test for transfusion-associated infectious agents

Introduction

Antibody to hepatitis B core antigen (anti-HBc) is a marker of past or current infection with hepatitis B virus. Its prevalence in any population is therefore directly correlated with the risk of HBV infection in that population. The presence of anti-HBc is also indirectly correlated with other diseases; specifically, non-A, non-B hepatitis and AIDS. It is reasonable to suppose that such correlations reflect the existence of common risk factors for infectious agents transmitted by parenteral or mucous membrane routes. More than 80% of AIDS patients and male homosexuals judged to be at high risk of developing AIDS, are reactive for anti-HBc. At a recent meeting of the Blood and Blood Products Advisory Committee to the OoB, it was suggested that appropriate implementation of anti-HBc screening could reduce the number of infectious agents introduced into source plasma pools. It seems likely that any measures adopted by the fractionation industry would also be implemented by whole blood collection agencies. This paper will evaluate some of the aspects of implementing the anti-HBc test on all whole blood collection operations in the American Red Cross.

Prevalence of anti-HBc among Red Cross donors

The overall prevalence of anti-HBc has been evaluated in a number of studies on routine donors: The results are summarized below.

Table 1: Prevalence of anti-HBc among Red Cross donors

Study Reference	Number tested	Number positive	% positive	Regions represented
1	20,643	453	2.2	Bostn, Frmtn, Phila
2a	1,647*	31	1.9	Birmg, Mdsn, Burln, Wchta, Tucs
2b	330**	12	3.6	" " " " "
3	335	17	5.1	Bostn, Los A, Phila, Charl, Detrt, Cleve, Wash, DC, Birmg
4	1,650***	114	6.9	Los A
5	14,591***	590	4.0	Buflo
Overall	39,196	1,217	3.1	

* Donors selected for normal ALT levels (96.8% of all donors)

** Donors selected for elevated ALT levels (3.2%)

*** Samples taken after implementation of AIDS screening measures

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The prevalence of anti-HBc varies inversely with sociodemographic status. We have found, in studies on 1,676 random donors, identified in Burlington, Birmingham, Wichita, Madison and Tucson, and selected for normal ALT levels, that 2.5% of males and only 0.9% of females are reactive. In the same study, 1.5% of white, and 9.3% of black donors were anti-HBc reactive. It has also been shown that anti-HBc is found among 3.6% of donors with ALT elevations; a significant increase relative to normal donors. However, it must be remembered that ALT elevations occur only among 3% of donors.

Costs

Abbott Laboratories is the only current supplier of a licensed test for anti-HBc. I have been advised that the test will be priced on a sliding scale basis ranging from $3.55 per test for 1 to 1000 tests monthly to $1.55 per test for more than 25,000 tests/month. Given that, an average, Red Cross regions draw around 10,000 bloods/month, it is reasonable to estimate an overall cost of $2.00 per test. This figure should be increased by 10% to account for controls, repeat testing and wastage of reagents.

The direct costs of applying this test may be estimated using the approach taken in the study on costs of ALT (6), and assuming a discard rate of 3%.

Table 2

Direct costs of anti-HBc testing

Item	Item cost	Number of items incurred/1000	Total direct costs/1000
Reagent cost	$2.20	1000	$2,200
Personnel	0.30	1000	300
Administration/ record keeping.	0.70	1000	700
Cost per unit discarded	50.00	31	1550
Marginal recruitment	4.00	31	124
Notification of donors	3.00	31	93
Second cycle effects	--	30	147
Total			5121

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Thus, the initial year of testing would be expected to add slightly more than $5.00 to the direct cost of producing a unit of blood. This calculation is sensitive to a number of assumptions such as the overall reactive rate and the marginal cost of donor recruitment. A cost-benefit analysis could be modeled on

the ALT study, if there was a firm basis for predicting the amount of disease prevented by the implementation of testing. It might also be argued that anti-HBc testing would serve to reduce the incidence of Posttransfusion hepatitis. In the case of hepatitis B, it is unlikely that the effect would be measurable. The range of estimates of direct cost savings for non-A, non-B hepatitis prevention could range from $1.22 to $14.56 per blood unit, assuming a 12% prevention rate (7), and 28 cases of hepatitis per 1000 recipients (6). As explained elsewhere, low estimates appear more realistic for a purely voluntary donor resource; thus, net benefits would probably be negative.

Rejection rates

The anti-HBc reactivity rate has been estimated on the basis of point-prevalence studies representing a cross section of the total donor population. However, as with HBsAg testing, it would be anticipated that as a result of testing, the repeat donor population would be depleted of reactive donors. Eventually, the detection rate would become stable, representing a combination of the prevalence among first-time donors and the incidence among repeat donors. We have found that first-time and repeat donors do not currently differ significantly with respect to the prevalence of anti-HBc. We have also shown that repeat donors acquire HBsAg at a rate of 66/100,000 annually (8) which can be taken as the lower limit of incidence of HBV infection. As an upper limit, this seroconversion rate could indicate 660 infections per 100,000 annually, since 10% of HBV infections lead to the HBsAg carrier state. Assuming 17.1% of collections are from first-time, and 82.9% from repeat, donors and that donors give 1.6 times per year it can be estimated that the anti-HBc detection rate would tend to stabilize at between 0.5 and 0.9%. However, it is unlikely that these low values would be achieved in practice.

Logistics

1. Test availability. Abbott Laboratories is currently the only vendor of a licensed test for anti-HBc. Representatives of Abbott assure me that there is sufficient production capacity to supply the entire testing needs of the blood and plasma collection complex in the United States. Further, this capacity could be realized within 30 days. There is real potential for additional manufacturers to provide competitive anti-HBc tests within the next one to two years.

2. Test protocol Currently, Abbott provides radioimmunoassay and enzyme immunoassay procedures for anti-HBc. The radioimmunoassay procedure is based upon an overnight incubation protocol whereas the enzyme procedure uses either a 2 1/2 hour, or an overnight protocol. Both procedures are inhibition immunoassays: they do not provide an unequivocal interpretation. The cutoff value is based upon a 50% inhibition estimate. The precision of the enzyme test around the cutoff value is between 7 and 10%; a value which would cause considerable difficulty in interpreting the values of repeat tests. The test procedure is relatively simple, but is much more dependent upon accurate pipetting than is the test for HBsAg.

Other aspects

1. Hepatitis B vaccine. Extensive use of the hepatitis B vaccine among groups at risk of HBV infection would completely negate the value of anti-HBc as a marker of those at risk of parallel infections: this consideration should be remembered when an AIDS-related test is selected.

2. IgM-anti-core. A subclass specific test for IgM-anti-core is available. Its use should perhaps be considered.

3. Combination test. A test which can be used for the simultaneous detection of anti-HBc and and HBsAg is available in Europe and has been evaluated in Canada. It appears comparable in performance to the individual tests. However, it requires both a spectrophotometer and a gamma counter.

4. Can anti-HBc replace HBsAg testing? The majority of HBsAg reactive samples are reactive for anti-HBc. Unfortunately, some 4% of all HBsAg-reactive samples are non-reactive for anti-HBc, and presumably represent early infection. Therefore, anti-HBc could not replace HBsAg testing.

References

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7. Holland, P.V. In Szmuness, W., Alter, H.J. and Maynard, J.E. Viral Hepatitis, 1981 International Symposium. Franklin Institute Press, Philadelphia, 1981, p. 563

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EXHIBIT G

Joint News Release
June 22, 1983
American Red Cross
American Association of Blood Banks
Council of Community Blood Centers

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The nation's voluntary blood service organizations today announced they do not advocate "directed donation," an unconventional practice whereby patients needing transfusions select their own blood donors. The American Red Cross, American Association of Blood Banks and Council of Community Blood Centers agreed that existing arrangements with volunteer donors and donor groups are the best way of assuring a safe supply of blood for all patients needing transfusions.

Publicity about the current AIDS epidemic has led to widespread concerns about the possibility of transmitting AIDS through blood transfusion. The facts do not justify these concerns: data accumulated over the last three years indicate that the possible occurrence of AIDS in transfusion recipients is on the order of one case per million patients transfused. Still, as a consequence of misleading reports, some patients have demanded that blood for their transfusions be donated by specially selected family members, friends or co-workers.

The three organizations emphasize there is no scientific basis for the assumption that blood from donors selected by patients is safer than that available from volunteers at community blood banks. In fact, such a practice may be hazardous because it could pressure selected donors to be untruthful about their ability to meet donor eligibility requirements.

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ARC, AABB and CCBC all agree that the altruistic volunteer donor who is free from coercion or expectation of gain is the safest blood donor. As a further precaution, blood centers across the country have recently adopted even stricter requirements for blood donation to assure that high risk donors are excluded.

Adopting a policy of patient-directed donations would create an illusion of additional protection where none exists and, by disrupting existing volunteer donor systems, could result in inability to supply blood to patients who need it. The blood collecting organizations are also concerned that the logistical complexities of patient-directed donation could lead to serious errors in donor and patient identification.

ARC, AABB and CCBC represent some 2500 community and regional blood centers, hospital blood banks and transfusion services which collect and transfuse over 98% of the nation's blood supply.

# # #

EXHIBIT I

TO: AIDS Working Group
Dr. Dodd
Ms. Baum

DATE. 3/20/84

FROM: Dr. Cumming

SUBJECT: Meeting request and report on: Progress on AIDS marker testing marketing research

SUMMARY

Our review of AIDS marker testing issues to date brought into question the value or continuing to proceed along lines or developing a non scientific opinion research survey. Specifically:

* objectively it is difficult to make a case for adoption or AIDS marker testing,

* plasma industry projected adoption or such a test is a rather obvious marketing initiative which will serve to increase pressure on us, and

* ARCBS decision-making criteria are complicated by considerations of ethics and public welfare as distinct from competitive response.

This last issue can be summarized nicely by reference to "false positives". Essentially all anti core test results are likely to be false positives. Specifically, it is estimated that over 6,000,000 annual units are donated by 4,000,000 persons. With 5% normal population incicence of anti core positive results this means 200,000 people may be labelled as likely to get AIDS. Contrast this with a possible 50 cases per year or AIDS avoided (0.00025 of all positives). Assuming these 200,000 people have additional testing done, costs to society may be from $20,000,000 to $100,000,000 (based on $100 to $500 per false positive). And this does not ascribe any value to mental anguish, time off work, etc. These figures and issues make the direct cost of testing minimal in comparison.

It is from this perspective that we question the value of continuing to develop a non projectable sampling effort and request a meeting to clarify as precisely as possible where we

are heading and why.

BACKGROUND

Attached for your information, review, and comment are:

1) a background document summarizing various marker tests for AIDS, and estimating effectiveness and costs, and

2) three draft questionnaires designed to elicit the opinions of various interest groups on marker tests for AIDS.

The background document explores some of the costs and benefits of implementing screening marker testing for AIDS amongst blood donors. On the descriptive matrix, characteristics such as effectiveness, ease of use, availability, etc. are estimated, as well as other potential advantages and public relations effects.

The latter is an area of grave importance which must be further explored. As you are aware, the possibility exists of creating panic in the (normal) donor population from positive test results, and incurring unnecessary costs to the health care sector as these donors pursue further medical evaluation, as well as reducing the size of the donor pool. These effects must be carefully weighed against the possible benefit of reassuring the blood recipient population and the hypothetical benefit of reducing the incidence of transfusion-associated AIDS (tfx-AIDS).

The cost matrix addresses the potential costs associated with implementation of the various marker tests. Review of this matrix indicates that costs for testing in all ARC Blood Service regions would range from $15M to $67M. If we assume that each averted AIDS case has a value of $1M, then to justify use of one of the tests would require an expected reduction in tfx-AIDS from ARC blood of 15 to 67 cases. Since tfx-AIDS patients have averaged 30 years of age, average earnings per worker are approximately $20,000 per annum, and treatment for AIDS victims has averaged about $80,000, the likely value of an averted tfx-AIDS case is about $500,000. This lower benefit would indicate a need to prevent 30 to 134 tfx-AIDS cases from ARC blood to justify use of a marker test exclusively on economic considerations. In addition, these averted cases would have to be over and above the number of cases prevented by currently implemented screening measures.

As an example, to economically justify anti-HBc testing in all Blood Service regions, we would need to demonstrate an anticipated rate of tfx-AIDS (not prevented by screening measures) of 1.75 cases per week, assuming an 85% effectiveness rate of the test. This rate is considerably above previous and

current rates.

PROPOSAL

To summarize the background document, implementation of any AIDS marker test will be extremely expensive. Given the fact that tfx-AIDS is still a hypothesis, that there has been no effective measurement of the success of the screening procedures which have already been implemented, and that cost justification of testing would rest on a considerably higher incidence of tfx-AIDS than is currently being observed, the following recommendations are proposed for further exploration.

1) implement the confidential self-exclusion procedure, currently used by New York Blood Center (NYBC), in all ARC Blood Service regions.

2) implement one of the marker tests in Los Angeles and any other regions where there is reason to suspect a high concentration of AIDS carriers.

3) continue to evaluate the non-economic considerations inherent in implementing one of the marker tests systemwide.

It is in keeping with the last recommendation that the three questionnaires are attached. The non-economic considerations are primarily the opinions and beliefs of the various publics which are served by ARC Blood Services. The questionnaires which are attached are targeted at physicians who prescribe blood, the general public including blood donors and recipients, and third party payers such as Medicare/Medicaid agencies and insurers. We intend to modify or add to these questionnaires to also target hospital administrators and other signatories of annual hospital/blood region contracts.

Relative to these questionnaires, we would appreciate information or comments on the following:

* decision making criteria given results of the survey, i.e. what influence will the results of the survey have on a decision whether or not to implement marker testing?
* method of sampling and sample sizes
* content and phrasing of questions
* target audiences

PURPOSE OF MEETING

Answers to this first question are essential for further development of the survey. Obviously if public opinion could determine that ARC implement testing, a very large sample would be required, whereas if the questionnaires are designed merely to "test the waters", a small screening sample would suffice. At this point, we really can't see too much value in a small, non-scientifically projectable sample. For such a sample to be useful for other than field testing of an instrument, we would have to observe a high degree of unanimity of opinion. Given the subject matter this is unlikely. For a large and statistically valid and reliable sampling effort to be most useful, we need to be very specific as to how we intend to use results from each likely outcome of the sampling. I suggest that a meeting of the group plus Dr. Dodd and Ms. Baum is in order to gain this specificity or select another course of action.

EXHIBIT J

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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ADVISORY COMMITTEE
BLOOD PRODUCTS ADVISORY COMMITTEE
27TH MEETING

8:30 a.m.

TUESDAY, OCTOBER 31, 1989

Ramada Inn
8400 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING CO., INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

There is one other point that is ancillary to that, as I think that we have all been aware that we need to moderate the appropriate use of blood and accentuate that.

I think that if the physician took the additional responsibility that there was a post-transfusion sample necessary, that would be a powerful incentive to moderate the inappropriate use of blood which is something that we have been advocating for some time with minimal to moderate effectiveness.

I think the time has come to rethink that lookback, while it will identify some individuals, we can do much better than that.

Thank you.

DR. ALVING: Thank you, Dr. Simon. Are there any other comments before we go on to the next issue of testing in-source plasma? Please come forward and identify yourself.

DR. ALLER: I am Ray Aller. I am a community blood banker from Santa Barbara, California. I see that there are a number of very complex issues here which I, obviously, don't completely understand.

But it seems to me in our society, we have limited resources. In terms of how we are going to allocate those limited resources that are available to the blood banks, to make sure we discover as many of the patients that may have

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come in contact with this virus through blood transfusion, as a national policy, it may be more effective to encourage the public, who know they have been transfused or whose physicians know they have been transfused, to seek testing.

I am concerned that, as a national policy, the paperwork trail is so long and tenuous, that it, really, would not give us a very high yield to do lookback.

That is in terms of a national policy. Unfortunately, when we are dealing with patients, we are not dealing with statistics. There are some blood banks that, actually, have a very good and very inexpensive system for finding the patients who received our blood.

We have always, because we had a credit system, maintained a record of every patient who received every unit of our blood, as a regional blood bank. We have many of those records, yet. It is not difficult for us to identify who those patients are, not costly for us. Of course, there are clerical errors and so on.

I admit, I am going to have an ethical dilemma when I find my first few donors that are hepatitis C positive, and they have been donors in the past, I would have a real ethical problem, I think, if I didn't make some effort to try to contact those patients.

But, at the same time, there is the issue of the community standard. If I do that, am I putting my colleagues

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in other blood banks that don't happen to have such a cross-check record, at legal risk because I can do it easily and inexpensively, and they can't.

There are a lot of questions I don't know the answer to. As a physician, I have a lot of concerns about this area. But the question, in terms of notifying the donors, right now, we don't know much about treatment. Certainly, there are some, at least, palliative sorts of things that can be given to people with these sorts of diseases to slow down the progression to cirrhosis -- steroids and this sort of thing.

I am not a gastroenterologist, but if I were infected with this virus, I think I would want to know there is a potential of, possibly, slowing the progress. So there are some real ethical dilemmas that, I think, need to be dealt with by wiser heads than mine.

Thank you.

DR. ALVING: Are there any other comments? Yes?

DR. SAYERS: Merlin Sayers, CCBC. I would have to support the proposal that the lookback is not the responsibility of blood programs. I think there are two compelling reasons why that is a reasonable assessment.

One has to do with the fact that this is not a new epidemic. This is not a new disease.

Mr. DINGELL. The subcommittee will come to order. The Chair announces that this is a continuation of hearings earlier held with regard to the safety of the blood supply and measures to assure that it is kept at the highest levels possible with regard to safety, quality and lack of risk to the American people.

The Chair announces that we have reconvened in response to the Chair's earlier comments with regard to the time at which the subcommittee would meet. The Chair announces that our panel this afternoon is Ms. Mary T. Carden, National Expert Investigator for Biologics for the Food and Drug Administration, the Buffalo District Office.

Ms. Carden, we thank you for being present with us. We appreciate your assistance to us. The Chair notes that you are accompanied by Mr. Pitt Smith, who is the Director of the Buffalo District Office. Mr. Smith, we welcome you and we thank you for being with us today, too. We will look forward to such assistance as you choose to give to the committee as we proceed with our business.

Mr. Smith and Ms. Carden, the Chair advises that it is the practice that all witnesses before the committee testify under oath. The Chair inquires; do either of you have any objection to testifying under oath?

Ms. CARDEN. No.

Mr. SMITH. No.

Mr. DINGELL. The Chair advises that, given that circumstance, it is your right to be advised by counsel, should you so choose. Do either of you desire to be advised by counsel in connection with your appearance today?

Mr. SMITH. No.

Ms. CARDEN. No.

Mr. DINGELL. Very well. The Chair advises that copies of the rules of the House, the rules of the committee and the rules of the subcommittee are there before you in the red and blue booklets which you see there at the table before you. The Chair advises that if you have no objection then, would you each please rise and raise your right hand?

[Witnesses sworn.]

Mr. DINGELL. The Chair has been advised that you have no statement, so the Chair will therefore recognize Mr. Sims, counsel to the subcommittee, for purposes of asking questions.

Mr. SIMS. Thank you, Mr. Chairman. I would obviously invite the members to interject at any point. The only reason we are doing this is the lateness of the hour and the fact that most of the questions are simply of a technical nature.

Ms. Carden, how long have you been with the FDA and how long have you been a national expert?

TESTIMONY OF MARY T. CARDEN, NATIONAL EXPERT INVESTIGATOR FOR BIOLOGICS, BUFFALO DISTRICT OFFICE, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY PITT SMITH, DISTRICT DIRECTOR

Ms. CARDEN. I've been with the FDA since September of 1978.

Mr. SIMS. Excuse me. Could you pull the mike a little closer to you, please?

Ms. CARDEN. I've been with FDA since September of 1978 and I started in the Orlando District Office and I became the National Expert in Biologics in September of 1988.

Mr. SIMS. I believe you're also an instructor at national training courses?

Ms. CARDEN. Yes, that's correct.

Mr. SIMS. Let me say on behalf of the subcommittee that your reputation precedes you and we're very, very pleased to have you with us today. Could you provide us with some background as to why you were selected to perform this investigation? I note that you're from the Buffalo region, but yet you performed an investigation here in the Nation's Capital.

Perhaps at the same time, you could explain to us why the FDA decided that it should do an investigation of the Red Cross National Headquarters?

Ms. CARDEN. As the National Expert, I am located in the Buffalo District Office, but I actually work for the Division of Field Investigations in Washington, D.C. Therefore, I do a number of inspections across the country.

One of the inspections that I've conducted in the past was of the Albany Region of the American Red Cross. That was at the request of the Buffalo District. As a followup to that inspection of the Albany Red Cross, I was then asked to conduct an inspection of the National Red Cross here in Washington.

Mr. SIMS. As I recall, the Albany center was one that has had problems discovered and has either been shut down or is in the process of being shut down?

Ms. CARDEN. The inspection that I conducted began in December of 1989, and as a result of the inspection, the American Red Cross was sent a letter of notice of intent to revoke their license, or rather to institute proceedings to revoke that license. To my knowledge, currently the American Red Cross is going to shut down that region and consolidate the operation with the Syracuse Region.

Mr. SIMS. Let me ask a general question here. Are Red Cross regional blood centers required to report errors and accidents to the FDA?

Ms. CARDEN. Yes, they are.

Mr. SIMS. In your opinion, based on the findings of your investigation at the National Red Cross—did the Red Cross make these reports promptly to the FDA?

Ms. CARDEN. Not in all cases, no.

Mr. DINGELL. Ms. Carden and Mr. Smith, the Chair would like to direct this question to you at this time: You said that they are required to report?

Ms. CARDEN. They are required to report errors, yes.

Mr. DINGELL. Is that by FDA regulation or by statute?

Ms. CARDEN. By FDA regulation.

Mr. DINGELL. That regulation is issued pursuant to statutory authority of the Food and Drug Administration?

Ms. CARDEN. I believe so.

Mr. DINGELL. Thank you.

Mr. SIMS. Thank you, Mr. Chairman. Isn't it also true that the Red Cross' own internal operating procedures require them to make such reports?

Ms. CARDEN. That's true.

Mr. SIMS. What, in your opinion, would be a prompt report, to use the term in the Code of Federal Regulations itself?

Ms. CARDEN. My definition of prompt would be 10 to 15 days.

Mr. SIMS. But you found in your inspection, as it is stated—and let me ask, Mr. Chairman, that Exhibit K be placed in the record at this time, which is the summary of your inspection.

Mr. DINGELL. Without objection, so ordered.

[The document follows:]

EXHIBIT K

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 900 Madison Ave. Baltimore, Md. 301-962-3396
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Lewellys F. Barker MD	DATE OF INSPECTION: 4/26/90-5/25/90 / C. F. NUMBER
TITLE OF INDIVIDUAL Responsible Head	TYPE ESTABLISHMENT INSPECTED Blood Bank
FIRM NAME American Red Cross National Hdq.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS 1730 E.St. NW	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE Washington, DC 20006	CITY AND STATE Same

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

ERROR/ACCIDENT REPORTS

1. In January, 1990 North Eastern Pennsylvania Region identified blood components which were distributed,that had been collected from donors who were previously reactive for HBsAg and confirmed positive. As of 5/22/90 the region has not notified the transfusion services as required by BBD 4.9. An error report was completed by the region which indicates the error was discovered November 1989. The error report was not submitted to Regulatory Affairs until 3/14/90. This report has not been submitted to FDA.

2. There are approximately 386 Error and Accident Reports submitted by the various regions which have never been reviewed by Regulatory Affairs. For example:

a.) An Error Report from Tidewater Region dated 5/15/88 was received in Regulatory Affairs on 3/14/90, and is still awaiting review by National. The error involved 15 elevated ALT's shipped to the Swiss Red Cross.

b.) An Error Report from the Atlanta Region indicates that the error was discovered 2/20/90 and was received by Regulatory Affairs 4/3/90. The report is still awaiting review by National. The error involved a donor that should have had a deferral code X/L however a code H was not updated to the X/L. The H was deleted in error when IBIS/RBIS system could not recognize a new decade.

c.) An Error Report from South Western Michigan Region indicates the error was discovered 2/7/90 and was received by Regulatory Affairs 3/28/90 and is still awaiting review. The error involved products being released from anti-HIV reactive,Western Blot negative donor who was not identified by the donor deferral system.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE: Mary F. Carden	EMPLOYEE(S) NAME AND TITLE (Print or Type): MARY F CARDEN, INVEST. ASST.

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3. Error reports are not always being submitted by the Regions to Regulatory Affairs in a timely manner, nor are the error reports reviewed and submitted to FDA in a timely manner. For example:

a.) An Error Report from the Appalachian Region indicates an error was discovered 10/4/88 and was reported to Regulatory Affairs 10/26/88 involving a donor notifying the center her husband had had multiple sex partners some of whom were at high risk for aids. Regulatory Affairs signed the report 3/9/90 however it has not yet been reported to FDA.

b.) An Error Report from the Connecticut Region was discovered and reported 3/26/87. The error was submitted to Regulatory Affairs 4/7/87 however the report was not submitted to FDA until 7/11/89. The error involved an anti-HIV reactive donor (Western Blot Indeterminate) whose deferral code was not updated to a category 8 and products were released.

c.) An Error Report from the Central Texas Region indicates an error was discovered 1/11/89 and was not submitted to FDA until 8/2/89. The error involved the release of products from a donor anti-HIV reactive.

d.) An Error Report from the Appalachian Region indicates there was a transfusion reaction due to Salmonella contamination of the blood products which occurred 9/1/89 and was reported to Regulatory Affairs 9/6/89. The recovered plasma was recalled from the fractionator on 9/6/89. The error report was returned to the region 2/9/90 for signature and has not yet been submitted to FDA.

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e.) An Error Report from the Appalachian Region indicates on 10/26/88 the region was notified by a donor that they had been in contact with an individual who has now been diagnosed with aids. The report was received by Regulatory Affairs 11/8/88 and was returned to the region for additional information on 3/8/90. Two of the components were recalled and destroyed. The error report has not been submitted to FDA.

f.) An Error Report from SE Michigen, which involved bacterial contamination of platelets and subsequent death of the recipient and the recall of additional products was received in Regulatory Affairs on 2/26/90. As of 5/4/90 this report has not been submitted to FDA.

g.) An Error Report from Chesapeake Region indicates the error was discovered 8/22/89 and the report was received in Regulatory Affairs on 2/23/90. This error report indicates there was bacterial contamination of components and the recipient subsequently died. As of 5/4/90 this report has not been submitted to FDA.

h.) An Error Report from Chesapeake Region indicates the error was discovered on 1/24/90 and the report was not received in Regulatory Affairs until 2/23/90. This error report indicates there was bacterial contamination of the platelets and the recipient subsequently died. As of 5/4/90 this report has not been submitted to FDA.

i.) An Error Report from Chesapeake Region indicates the error was discovered 4/9/90 and the report was not received by Regulatory Affairs until 5/17/90. This error report indicates there was bacterial contamination of the platelets and the recipient subsequently died. This report has not been submitted

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	Craig F. Carden	CRAIG F. CARDEN, INVEST.

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to FDA.

j.) An Error Report from Penn-Jersey Region indicates the error was discovered 11/29/89 and the report was not received in Regulatory Affairs until 3/13/90. This error report indicates there was bacterial contamination of the platelets resulting in an adverse reaction in the recipient. As of 5/4/90 this report has not been submitted to FDA.

4. The SOP for handling Error and Accident Reports by Regulatory Affairs has not been revised since July 1981 and there is no indication who reviewed and approved the SOP. The SOP is inadequate for the following reasons:

a.) the procedure does not designate the individual responsible for reviewing the reports submitted by the regions;

b.) the procedure does not provide a means of accounting for reports, for example a log indicating which reports have been received from the regions and which reports have been submitted to FDA;

c.) the procedure does not designate a time frame for review and submission of the reports to FDA;

d.) the procedure does not provide for any summary and analysis of the error reports to assure adequate correction has been instituted by the Region and to determine the need for any further corrective action by National.

5. Several copies of error reports and or investigations and background documentation submitted by the Regions and reportedly submitted to FDA could not be located and had to be

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faxed for the purpose of this inspection. Examples include: 8/28/89 submission to FDA-Central Texas Region, 12/26/89 submission to FDA-Carolina Lowcountry, 1/23/90 submission to FDA-Chesapeake Region.

6. Numerous Error Reports reviewed did not provide sufficient information to determine the cause of the error or an adequate description of the corrective actions taken.

7. There are approximately 230 reports of TAA transfusion associated AIDS reported to the Washington Region, however records indicate only four of these cases have been reported to National ARC as required by BBD 4.9. None of these cases have been reported to FDA as errors or accidents as required by BBD 4.48.

8. There are no procedures for reviewing and tracking transfusion associated AIDS cases by National to assure all regions are submitting the initial reports and follow up investigations are complete.

<u>BOP's</u>

9. Currently directives are issued to the Regions in the form of BBD's, BSL's, BSM's, Operations Bulletins, Regulatory Affairs Bulletins, and from Information Services in various forms including IBIS Documentation Bulletin's. BBD 1.56 is inadequate in that is does not address Operations Bulletins, Regulatory Affairs Bulletins and the Bulletins provided by Information Services. The BBD 1.56 does not provide for clear lines of control between Regulatory Affairs, Information Services and Operations, when issuing these directives to assure the directives are clear, accurate and meet Federal regulations. This is no evidence of review and approval by designated individuals of these directives.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Mary F. Carlen	EMPLOYEE(S) NAME AND TITLE (Print or Type) MARY F. CARLEN, INVESTIGATOR

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10. There is no SOP for the preparation and approval of Operations Bulletins. Information in Operations Bulletins often give instructions to Regions to write or establish SOP's. Directives provided in the Operations Bulletins are not enforced by National's BSQRA program.

11. There was no written approval by FDA for the implementation of the policy in Operations Bulletin #24. Operations Bulletin #24 dated 10/13/89, instructed Regions they were not to conduct a look back for blood products already released which at the time of donation met all testing requirements but during review were identified to be from a donor who had a past history of risk behavior, prior history of reactive test results, or a history of hepatitis. There was no correction issued to the Regions regarding this policy in Operations Bulletin #24 until 5/11/90 despite the fact ARC was informed in January 90 this policy was unacceptable.

12. There are several procedures in place for handling recalls of Recovered and Source Plasma. These include: a document titled Standard Operating Procedure for Recovered and Source Plasma Recalls revised 11/89; a Memo dated December 7, 1989 on the Procedure for Release of Short dated ARC Products implicated with Erroneously Released Plasma; SOP for Withdrawal of Plasma Lots dated 7/8/88; a chart dated 9/7/88 and titled Types of Erroneous Releases- anti-HIV; and a memo dated 11/3/87 regarding BBD 6.23 attachment 2 Protocol for Shipment of Plasma Submitted for Fractionation. There is no record of the review and approval of these procedures.

13. There is no SOP for the review and submission of amendments to the establishment and product license including individuals responsible for preparing, tracking, reviewing and submitting the amendments to FDA.

14. An Establishment license amendment was not submitted to

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	Craig S. Candler	

FORM FDA 463 (8/82) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 6 OF 9 PAGES

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FDA regarding the transfer to the Syracuse Region of at least 60% of transmissible disease testing conducted by the Albany Region.

OPERATIONS BULLETIN #20

15. Operations Bulletin #20 did not provide sufficient instructions for conducting a search for 3 donor names which had been entered into the system with embedded spaces which would prevent them from being identified in the donor deferral system.

16. There was no documentation from the centers who had identified these donors as permanent deferrals (due to either confirmed hepatitis test results or Western Blot positive test results) that any subsequent collections from these donors were properly identified and destroyed.

17. The user documentation for the program Donor Surveillance where names are initially entered into the system does not address the fact embedded spaces are not to be entered. No change in the user documentation was issued by National to the Regions on the use of embedded spaces after the problem was identified and addressed in Operations Bulletin #20.

18. There was no instruction issued to Regions to review all records for donors names which contain embedded spaces to assure deferred donors would be identified in the local donor deferral system.

19. There was inadequate review of user documentation for the DS Verify Program distributed to IBIS users. Step #1.2 and #2.2 in the user documentation indicates the allowable characters for last names are the letters A thru Z, apostrophe, hyphen or space, which is in conflict with previous directions for entering last names in IBIS. Embedded

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Mary F. Carden.	EMPLOYEE(S) NAME AND TITLE (Print or Type) MARY F. CARDEN, INVESTIGATOR

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spaces and punctuation are not to be used for a donors last name when entered in the IBIS system.

COMPUTER ISSUES

20. The comprehensive evaluation of the RBIS/IBIS system done by Peat Marwick and reported and submitted to FDA on 10/14/88 listed specific modifications that needed to be made in the systems. As of the present date all of these modifications have not been made in the systems and some of the modifications have been developed but are not in place. Failure to implement one of the modification which required double key verification of manual test results resulted in several errors in the Albany Region.

21. When the Utility Programs were released in May 1988, there was no schedule for implementation of these programs by National. The purpose of these programs is to correct the databases specifically controlling the donor deferral system to prevent errors from being made. National ARC has not tracked which regions have implemented these programs to ensure follow up and corrections of records.

22. Utility Programs for the RBIS System have not been developed.

23. The user documentation for the Program Regdefer in the IBIS System does not specify procedures for deleting duplicate records in the databases. Correction of duplicate records was not performed by the Albany Region due to the lack of user documentation.

24. The user documentation for the program DDRLOAD in the IBIS system does not specify the requirement that the Regions are to review all reports generated including a report Verifying deletions of local deferrals nor are there any other

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (PRINT OR TYPE)
	Mary F. Barker	Mary F. Barker, Investigator

FORM FDA 463 (8/82) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 8 OF 9 PAGES

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

directives including a SSO. This lack of user documentation contributed to the failure to identify deletions of donors from deferral categories and the subsequent release of unsuitable blood products in the Albany Region.

25. Blood Services is not controlling installation of computer programs to assure Regions have installed programs and met time frames for implementation. For example the DS Verify program, Fixes and the Utility Program.

26. There is no responsibility at National ARC by Regulatory Affairs or Operations for controlling non standardized computer systems including review of computer validation protocols. There was no control or review of the Validation of the installation of the computer system utilized by the Charleston Region to perform Donor Surveillance. Failure to properly validate this system resulted in the release of unacceptable blood products.

27. Changes made to computer programs are not being properly controlled and reviewed. A change to the DDRLOAD programs resulted in the DDRPURGE program not deleting local deferral records that had a delete flag set.

28. Regulatory Affairs does not assure corrective action promised to the FDA in response to FD 483 citations is feasible and had been taken. Additionally regulatory affairs review of regional responses does not identify and control inconsistencies in the regional responses on similar 483 citations. These inconsistencies represent regional SOP's which are not standardized, and no corrective action is taken. For example the same problem was noted in FDA inspections of the Albany and Rochester Region in regard to the failure of the regions to document incubation times during transmissible disease testing. This same problem resulted in the release on unacceptable blood products by Buffalo Region.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Craig F. Carden	EMPLOYEE(S) NAME AND TITLE (Print or Type) CRAIG F. CARDEN, INVESTIGATOR

FORM FDA 483 (8/82) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 9 OF 9 PAGES

Mr. SIMS. You found that in many cases, errors were not reported to the FDA for a matter of months; is that correct?

Ms. CARDEN. That's correct.

Mr. SIMS. You also found in many cases that at the time of your inspection, errors had not been reported to the FDA at all; isn't that also correct?

Ms. CARDEN. That's also correct.

Mr. SIMS. In both cases, that would appear to be a violation, not only of the Red Cross' procedure, but of your regulations?

Ms. CARDEN. That's correct.

Mr. SIMS. What was the response of the Red Cross to your inspection?

Ms. CARDEN. I could characterize the general, overall tone of the inspection as very nonchalant. In my 12 years of experience in inspecting the blood industry as well as the drug and device industry, generally when I object to something during an inspection, the firm is very prompt at trying to provide some information for me to show that they've already corrected the deficiency or are going to do the best they can.

In the case of this inspection of the American Red Cross at National Headquarters, that type of attitude did not prevail. There were no promises of corrective action during the inspection. Other than the current Director of Regulatory Affairs, who had only been in that position for about 3 weeks at the beginning of the inspection, I did not see any expression of concern at all from anyone that I dealt with during the inspection.

Mr. SIMS. Did any Red Cross persons indicate to you that no matter how bad your findings were, that you should have seen it at a previous point in time; that things had gotten better than they were?

Ms. CARDEN. I'm sorry, can you repeat the question?

Mr. SIMS. Did any Red Cross person that you talked to in the course of this inspection indicate that whether or not what you found was bad that things had been worse previously?

Ms. CARDEN. Yes. In reference to my question about the lack, the failure to report the errors to FDA in a timely manner, I asked several people at Red Cross who were responsible for that why they had not been reported, to see if there was any good reason.

The response I got from the person who was immediately in charge of the error reports indicated that those error reports were not her first priority.

Another person I asked indicated that he probably shouldn't say this but the situation has been worse.

When I asked Dr. Barker, who is the responsible head for the American Red Cross, to whom this report was issued, he indicated that he had told them to get the situation corrected and what he indicated to me was he didn't intend for them to sit there, meaning the error reports for the rest of their life.

Mr. SIMS. Did you have a formal meeting with the Red Cross officials after your inspection and, if so, could you describe what transpired at that meeting?

Ms. CARDEN. At the close of any FDA inspection we always conduct a discussion with management and we're required to issue

this Form FD-483 that you have reviewed to the most responsible individual, which in this case was Dr. Barker.

I did hold that meeting and at that time the firm had many responsible individuals at Red Cross at that meeting. During that meeting I, as required, explained what my objections were again on all of the items that are listed on that form that you have, the FD-483. At this time, normally a firm will attempt to make some verbal response to me indicating we will get these items corrected or we have already done it. That type of response is normal.

Mr. SIMS. And what was the response of the Red Cross?

Ms. CARDEN. In this case they asked us, I was with a supervisory investigator from the Baltimore district office at the time, to leave the room so that they could discuss among themselves if they would like to respond at that time. When we were called back into the room, we were told that they would like to decline to provide a response at this time but would provide a written response at a later date.

Mr. SIMS. And based on the experience of your inspections, would you say this is usual or unusual?

Ms. CARDEN. I would say that in 95 percent of the cases a firm will respond during the inspection and certainly at the close of the inspection any item that I might consider objectionable.

Mr. SIMS. In fact, you told us yesterday that on a number of occasions in past inspections the inspected party has literally worked all night in order to correct the deficiency that you discovered, isn't that true?

Ms. CARDEN. That's true.

Mr. SIMS. But that certainly didn't happen in this case, did it?

Ms. CARDEN. Not to my knowledge. There wasn't a demonstration of it during inspection.

Mr. SIMS. Now when an error is discovered in a Red Cross regional blood bank, it is sent to the Red Cross national headquarters, is that correct?

Ms. CARDEN. Yes. As you know, all of the regional Red Cross Centers are under one U.S. license number and all those error reports go from the region to national headquarters, which is an acceptable system in that national should see those error reports so that they can review them and analyze them in case corrective action is needed nationwide.

Mr. SIMS. And the National Red Cross is supposed to provide those to the FDA, is that correct?

Ms. CARDEN. That's correct.

Mr. SIMS. Now when a regional Red Cross Blood Center sends an error report to the National Headquarters, does it provide a copy of that to the local FDA district office?

Ms. CARDEN. No, they don't.

Mr. SIMS. Why not?

Ms. CARDEN. I don't know why they don't.

Mr. SIMS. Do you think it would be a good idea if they did provide a copy?

Ms. CARDEN. Yes, it would.

Mr. SIMS. Would it help you somewhat?

Ms. CARDEN. Yes. It would definitely help.

Mr. SIMS. How would it help you?

Ms. CARDEN. I would have the error reports when I went to do the next inspection of that firm because when a district office received that error report they would file it in the establishment inspection jacket for that firm and then the investigator that was going to do the next inspection would have that immediately available to them without any delay.

Mr. SIMS. So it would help you when you did your annual inspection?

Ms. CARDEN. Yes.

Mr. SIMS. If the district office did not comply with the regulation to send an error report forward and in fact didn't create an error report, it would seem to me from what you have just said that there really is no way to double-check that process.

Is that a fair understanding of the system here?

Ms. CARDEN. You mean the regional ARC Blood Center?

Mr. SIMS. Yes.

Ms. CARDEN. If they did not create an error report? One of the purposes of the inspection by the FDA investigator is to determine during the inspection if there were any errors and if those errors were reportable, and were they sent into FDA.

In this case, if you are sitting in a regional Red Cross Blood Center, the only thing you can determine at that time is that that error report went to national headquarters.

Mr. SIMS. But if you had a copy of the error report, you could more quickly and more effectively check on the regional Blood Center, couldn't you?

Ms. CARDEN. That's correct.

Mr. SIMS. And if they knew that you had a copy, do you think that they would be more likely to promptly and accurately report these errors up the line?

Ms. CARDEN. Well, I believe your first question was if they submitted it to the district office as well, all right?

Mr. SIMS. Yes, that's the presumption.

Ms. CARDEN. Right.

Mr. SIMS. So you think that would be a good idea?

Ms. CARDEN. Yes, I do.

I think that what I have seen in some cases is that the regions are submitting the error reports to national headquarters but national is not passing them on.

You also indicated there is another problem in that that region may not submit the error report to begin with.

Mr. SIMS. Yes. Mr. Smith, as District Director, do you know whether or not your district is getting all the copies from FDA here in Washington of the error reports that make their way to the FDA here?

Mr. SMITH. I don't know if we're getting all of them. We only get a few every year, sporadically.

Mr. SIMS. So if your inspectors in the district got copies when they started up the line, you would certainly be more able to know whether you were getting everything through the headquarters when it came down the line, and this would be a rather nice double-check, wouldn't it?

Mr. SMITH. Well, yes, and it would serve as a prompt to us to conduct the inspection.

Mr. SIMS. So essentially what we are talking about here is an honor system. Would you concur in that statement?

Ms. CARDEN. I wouldn't characterize it as an honor system because during the FDA inspection an investigator would be looking for any errors that had occurred. That was the means by which hopefully we would find out that they hadn't submitted an error report.

Mr. SIMS. When you did your inspection, as we will discover in a minute, you found, number one, the regions had not sent error reports to the national headquarters as required; number two, the national headquarters had not investigated these reports as they should; and number three, the national headquarters had not sent the reports to the FDA headquarters as they should have.

Is that correct?

Ms. CARDEN. What was your first statement?

Mr. SIMS. The region had not sent the reports——

Ms. CARDEN. During the inspection of the national Red Cross, I could not determine if some error reports had not been submitted to national from a region but I could determine that they were delayed in coming from the regional to national ARC.

Mr. SIMS. Let's turn now to the document itself and find out specifically more about what you found.

In paragraph 1 we're talking about an error and accident report. Specifically this case involves a donor whose blood tested positive for hepatitis and this test was confirmed positive by a second test, is that correct?

Ms. CARDEN. It was confirmed positive, yes.

Mr. SIMS. Now the blood from such a donor is not supposed to be used, even though it was used in this instance, isn't that correct?

Ms. CARDEN. According to the records that I reviewed at national ARC, some of the products collected from these donors were transfused.

Mr. SIMS. Well, if a donor's blood is not allowed to be used, could you explain to us why the donor was allowed to donate?

Ms. CARDEN. If a donor is deferred, the blood can be collected from the donor, however, it cannot be distributed. Therefore, once it is collected, they must sort through which products were collected from deferred donors and those which were not.

Mr. SIMS. So by allowing a deferred donor to continue to donate, even though the blood is not supposed to be used, this puts an extra burden on the accuracy of the accounting system; doesn't it?

Ms. CARDEN. It does cause additional problems, yes.

Mr. DINGELL. As a matter of fact, it imposes extra risk, does it not?

Ms. CARDEN. It poses extra risk, in that if the person was deferred, you are exposing the people collecting the blood to diseases. Yes.

Mr. DINGELL. Thank you.

Mr. SIMS. What went wrong that allowed the blood components to be distributed in this particular case?

Ms. CARDEN. I believe, in this particular case, there was no deferral code on the donor's records in the computer.

Mr. SIMS. The report notes that, while the error was discovered in November of 1989, as of your inspection in May of 1990, the Red Cross had not notified the FDA.

Now this is clearly a violation of FDA regulations, which require such errors to be promptly reported; isn't it?

Ms. CARDEN. Yes, it is.

Mr. SIMS. In this case, the regulatory affairs element in Red Cross Headquarters, had not notified the FDA over 4 months after receipt of the error report from the region.

Now you said earlier that, in your view, a reasonable reporting time is something on the order of 10 to 15 days; is that correct?

Ms. CARDEN. Yes, it is.

I think it is important to note that the Red Cross, or any blood bank could inform FDA of the error, without having it fully investigated yet; but once they've released blood products that are unacceptable, that error report should come immediately to the Agency. Of course, we would understand that it might take some time to investigate it to determine the cause.

Mr. SIMS. So the distribution of this contaminated blood product and the failure to promptly report the error were both violations of FDA regulations; is that correct?

Ms. CARDEN. Yes. That's correct.

Mr. SIMS. In paragraph two, your report notes that approximately 386 error and accident reports submitted by various regions, had never been reviewed by Regulatory Affairs. Is this a violation of the Red Cross' own standard—standing operating procedures?

Ms. CARDEN. They do not have a specified time in their own standard operating procedures, in which they would review them; but reviewing them myself during the inspection, I determined that some of them had been there for quite some time and therefore, they should have been reviewed by them and passed on to FDA.

Mr. SIMS. Some of these were 2 years old; weren't they?

Ms. CARDEN. I believe so.

Mr. SIMS. And they had not even been reviewed by the Regulatory Affairs element, much less passed on to the the FDA; isn't that correct?

Ms. CARDEN. That's correct.

Mr. SIMS. So, the FDA was absolutely unaware that these occurred, except if they had been discovered by an inspection of a—by a regional office?

Ms. CARDEN. That is correct.

Mr. DINGELL. Then the practical effect of this was to delay the establishment of an adequate policy at FDA, with regard to reporting, disclosure and levels of risk and peril and possible other curative actions; isn't that so?

Ms. CARDEN. I am sorry. Would you repeat that?

Mr. DINGELL. If Food and Drug is not getting information as to events which are occurring out there which are adversely impacting the safety of the blood supply, it has—it has lost the ability to make an adequate and speedy response to threats which might exist in the blood supply, or which might be associated with the blood supply; is that not the case?

Ms. CARDEN. That is the case. Yes.

Mr. DINGELL. Thank you.

Mr. WYDEN. Mr. Chairman, may I just ask one question, at this point?

This is very helpful. My question to you at this point is, in September of 1988, the Red Cross and the Food and Drug Administration entered into an agreement to address most of the issues that you are talking about.

Is it your belief that the problems that you have found in your inspection violate aspects of that agreement?

For example, just the first section stipulates that clear lines of control of the regional blood services be established.

Ms. CARDEN. To answer your question, yes.

Mr. WYDEN. That what you found did violate that 1988 agreement?

Ms. CARDEN. Yes.

Mr. WYDEN. OK.

Thank you, Mr. Chairman.

Mr. SIMS. Thank you Mr. Wyden.

In paragraph 2(a) of your report, you note that 15 units with elevated levels of ALT were erroneously shipped to the Swiss Red Cross.

Do we know whether the ALT levels were high enough to be dangerous or not?

Ms. CARDEN. I think I mentioned to you, without the records and the report in front of me, I am not sure if that information is even in that error report.

Mr. SIMS. OK.

What caused this blood product to be mistakenly released? Can you recall that?

Ms. CARDEN. No. I do not recall what the reason was, in this particular case.

Mr. SIMS. OK.

Did you see error reports that did not contain enough information in them so that you could tell whether the blood product was dangerous or not?

Ms. CARDEN. Yes, that is true.

Mr. SIMS. Did you find error reports that did not contain enough information so that you could really judge the seriousness of the error itself?

Ms. CARDEN. Yes.

Mr. SIMS. Did you find instances where the Red Cross Headquarters themselves, had to send the error reports back to a given region to get more information?

Ms. CARDEN. Yes, I did.

Mr. SIMS. In paragraph 2(b), the report describes an Atlanta donor that should have had an X/L code, rather than an H code.

I understand that an X/L code is a permanent deferral and that an H code means that the blood is to be held; is that correct?

Ms. CARDEN. That is correct.

Mr. SIMS. Can you explain how this mix-up happened?

Ms. CARDEN. This was an error report that we asked them to explain for us during the inspection.

When the blood is collected and tested and you first receive reactive test results, or you note any problem or suspect a problem

with the blood product, you would put what they call a code H on that particular blood product; which will, in the computer, prevent the product from being distributed.

In this particular case, there was what they refer to as a bug in the computer system, which had to do with the fact that there was a new decade, 1990 being the new decade; and what happened, because of the bug, was that an H code was posted to all of the products that they had collected. I don't know whether it was in the same day, or what it was.

In this particular instance, because of the bug in the system and all of the H codes that were on the products, they had to go in and manually delete those H codes, in order to be able to distribute the product.

What happened was that someone did not recognize the fact that one of those H codes was a legitimate H code. In other words, the product should not have been distributed.

So, due to the fact that there was a problem in the computer system, it caused that error.

Mr. SIMS. Now, the software system, as I recall, was one of the problems that the FDA had identified in previous inspections of Red Cross facilities around the country. This was one of the subjects of the 1988 agreement that was supposed to be fixed by the Red Cross. Is that your recollection?

Ms. CARDEN. That is correct.

Mr. SIMS. In paragraph 2(c), a donor with an HIV positive and a Western Blot negative test donated and the blood was used.

Is this a violation of FDA regulations?

Ms. CARDEN. Yes, it is.

Mr. SIMS. You are not supposed to use that kind of blood?

Ms. CARDEN. Right.

Mr. SIMS. I presume that blood from an HIV positive and a Western Blot test, indeterminate, as described in paragraph 3(b), should also have been destroyed?

Ms. CARDEN. That is correct.

Mr. SIMS. In paragraph 3(e), your report states that the region was—the Red Cross region was told that a donor had been "in contact" with an individual with AIDS.

Did the error report indicate what kind of contact this was?

Ms. CARDEN. No. It did not.

Mr. SIMS. Did the Red Cross have to go back and try to request further information to figure this out?

Ms. CARDEN. They had requested the region provide some additional information.

Mr. SIMS. When you reviewed this case, could you tell whether or not the blood had been released and whether or not it was contaminated?

Ms. CARDEN. I could not tell from the information in the error report.

Mr. SIMS. So the error report was deficient in detail?

Ms. CARDEN. Yes.

Mr. SIMS. Neither you nor, presumably the Red Cross, could tell from the information that you saw, whether there was a problem or not, in terms of infectious blood being released?

Ms. CARDEN. Neither myself nor anyone at National Red Cross. The region may have that information.

Mr. SIMS. In paragraph 3(f), a death in Michigan is described from contaminated blood.

This had not been reported to the FDA some 3 months later. Obviously—what is the obligation of the Red Cross to report in this particular case?

Ms. CARDEN. In this particular case, when they received information that there was some type of reaction, including and as serious as death, they would be required to investigate it to determine if, in the manufacture of the product, they had done anything incorrectly which caused it; as a follow-up to that, complete an error report and submit it to FDA.

I might add in this particular case that I believe that the Red Cross reported this particular error to the FDA verbally during the inspection.

Mr. SIMS. An amazing coincidence, no doubt.

The next three paragraphs recount deaths earlier in this year due to bacterial contamination in the Chesapeake Region. Yet at the time of your inspection in May, none of these three deaths, from the same region, had been reported to the FDA. Isn't that correct?

Ms. CARDEN. That is correct.

Mr. SIMS. Could this have been a potentially serious safety problem of which the FDA would have been unaware?

Ms. CARDEN. Yes, it could. This is one of the concerns to me as the error reports are not reviewed at National and analyzed. They should have recognized that there is something different here, in that there are three reports of deaths from one region. There is a lot of potential out there as to what could possibly have happened. It could have been one of the procedures they used; it could have been a contaminated lot of blood bags; it could probably be a hundred different reasons. And all coming from one region, they should have recognized that and begun some analysis of that.

Mr. SIMS. So clearly, we could agree that three deaths in one region from the same cause in a relatively short time is at the very least a cause for serious concern; it should have been reported promptly to the FDA, and should have been quickly investigated?

Ms. CARDEN. Yes, I would agree to that. I think that one of the things I would like to add in this case is, without looking at the records, in some cases, after the investigation is conducted, you can determine that the product was contaminated and therefore was the cause of death or the product was not contaminated, or at least you could not prove it was contaminated, and you do not know what the cause of the error was, or, in fact, you might be able to prove that it was not the product. And I do not know the status in each of these without looking at the records.

Mr. SIMS. And this kind of information is absolutely critical to the question of whether you need to do an immediate recall or not. Would you agree?

Ms. CARDEN. Yes, I would.

Mr. SIMS. And if there were contaminated product and it was not recalled promptly, there is at least the possibility, if not the probability, of further negative health effects; right?

Ms. CARDEN. That is correct.

Mr. SIMS. I notice in your report, that the SOP for handling error and accident reports at the Red Cross had not been revised since July of 1981.

Your inspection found that the SOP did not require that a particular individual be responsible for reviewing error reports. And it also found that a log or some other accounting system was not required to keep track of all these error reports.

Is that correct?

Ms. CARDEN. That is correct.

Mr. SIMS. In your opinion, did this contribute to the failure of the Red Cross to review regional error reports and pass them to the FDA in a timely manner?

Ms. CARDEN. Yes, I believe so. When you have that many regions reporting information in to you, I think it is critical that you have some system of tracking them from the time you receive them to the time that you submit them to FDA.

And I might add that, in terms of numbers, my understanding was that they might receive 100 a month, and some of the other figures that they gave me were they may receive zero one day versus 40 on another day. So I think the volume is sufficient that they definitely need a tracking system.

Mr. SIMS. So this kind of tracking and accounting system is elemental to assure an organization's ability to keep track of the reports. Would you agree?

Ms. CARDEN. It is basic quality control.

Mr. SIMS. And they did not have that in place when you did your inspection?

Ms. CARDEN. That is correct.

Mr. SIMS. Do you believe that this SOP should be revised and improved as soon as practicable?

Ms. CARDEN. I certainly do.

Mr. SIMS. Do you know whether or not that work is in place?

Ms. CARDEN. Not to my knowledge.

Mr. SIMS. You do know whether it is or is not?

Ms. CARDEN. No, I do not.

Mr. SIMS. In general, would you say it is a fair statement to characterize the Red Cross recordkeeping system as inadequate?

Ms. CARDEN. Yes.

Mr. DINGELL. As a matter of fact, Food and Drug Administration reports, and the Department of HHS Public Health Service reports, indicated exactly that, did it not?

Ms. CARDEN. I'm sorry, sir?

Mr. DINGELL. The recordkeeping, the property management computer system at FDA were all insufficient to meet the needs. Is that not so?

Ms. CARDEN. Which report are you referring to?

Mr. SIMS. Your 483.

Ms. CARDEN. My—yes.

Mr. DINGELL. This is your report.

Ms. CARDEN. Yes.

Mr. SIMS. In Paragraph 7, your report found that of approximately 230 reports of transfusion-associated AIDS reported to the Wash-

ington, D.C. Region, only four cases were reported to the American Red Cross Headquarters.

Could you explain how your inspection discovered these 230 reports and exactly what the Red Cross records show?

Ms. CARDEN. When we began the inspection, I was with two other investigators. One investigator was from the Baltimore District Office, and she had obtained a copy of a letter while inspecting a blood bank which was from Red Cross indicating they were looking for some units that had been distributed from a donor who was now Anti-HIV Repeatably Reactive and Western Blot positive. In other words, they were looking for a unit that had been collected previously from him.

We took that letter with us to National ARC and asked them what information they had about that letter. And their first indication was that they did not know about the situation. That particular situation or that product that was in question had been distributed by the Washington Region.

Mr. SIMS. Should they have known about it?

Ms. CARDEN. Yes.

Mr. SIMS. Please continue.

Ms. CARDEN. Since they did not have any records there, we asked them to call the Washington Region and find out, give us some information about the situation. And they indicated that they had some records there and that they would fax them to National ARC.

And the records that were faxed to us were approximately five pages of information. One of the pieces of information on one of the records said Case Number 169. Because it said Case 169, we asked if there were 169 cases. And they indicated that they did not know, but they would ask. And they asked Washington Region. And their response was there were, I believe the number that I was given was 230.

Mr. WYDEN. Would counsel yield for just a moment?

Mr. SIMS. Yes. Of course.

Mr. WYDEN. I appreciate it.

The Red Cross on July 10, Ms. Carden, put out a statement. One of the things that they said, talking about error and accident reports, I want to just quote to you.

They called them procedural errors which are corrected immediately at the local level and then routinely reported to National Headquarters which in turn reports them to the FDA.

Is that possibly a true statement?

Ms. CARDEN. Not to my knowledge.

Mr. WYDEN. I thank counsel.

Mr. DINGELL. If counsel would yield, how is that possible, in view of the level of recordkeeping, computer capability, and reporting that you found internally at the American Red Cross and also with regard to the reporting which goes on between the American Red Cross and Food and Drug?

How is that possible?

Ms. CARDEN. I am sorry——

Mr. DINGELL. First of all, you found internal deficiencies with regard to the reporting.

Ms. CARDEN. That is correct.

Mr. DINGELL. At American Red Cross.

Ms. CARDEN. Yes.

Mr. DINGELL. You found significant failures by American Red Cross to keep proper books and records.

Ms. CARDEN. That is correct.

Mr. DINGELL. You found failure of American Red Cross to keep an adequate and up-to-date computer system, properly maintained and upgraded. Is that not so?

Ms. CARDEN. That is so.

Mr. DINGELL. Now, in view of those facts, how is it poesible that American Red Cross could be conducting the program that they have indicated by requiring that the matter be reported quickly from the local units to the National Headquarters, and then from the National Headquarters to the Food and Drug Administration?

Ms. CARDEN. That is their statement. You will have to ask them about it.

Mr. DINGELL. In your view, it is not possible?

Ms. CARDEN. No.

Mr. DINGELL. Thank you.

Mr. SIMS. Thank you, Mr. Chairman.

I guess the point of this 230-case example is that Red Cross National Headquarters really had no idea about what had happened with these cases.

Is that a fair statement?

Ms. CARDEN. That is one of my main concerns. And as soon as they receive such a report in a region they need to conduct an investigation. And there should be records of investigations for all of those, and they should determine if there was any error involved And that error should then come to the Agency.

Mr. SIMS. So as we sit here today, we really do not know very much about these 230 cases; is that correct?

Ms. CARDEN. I do not know very much about those 230 cases. But there are people in FDA looking at those currently.

Mr. SIMS. Although they probably know a bit more about them now than they did then. Well I don't want to guild the lilly here. I would just note in my last question that it is true, isn't it, that your inspection found various problems with the computer software, such that the Red Cross could not assure that the blood of deferred donors would be stopped from being used? Is that correct?

Ms. CARDEN. I think it would be better characterized by saying that there were serious problems with their usage of that computer system as a whole, rather than specifying just the software.

Mr. SIMS. So it's more than just the software?

Ms. CARDEN. Yes.

Mr. SIMS. Those are all the questions I have, Mr. Chairman.

Mr. DINGELL. The gentleman from Oregon, Mr. Wyden.

Mr. WYDEN. Thank you, Mr. Chairman. I think we have covered it. Just a couple of other quick points, if I could. Ms. Carden, was the Red Cross slow to come up with programs designed to identify blood donors who were HIV positive and identify those who might have given blood?

Ms. CARDEN. I'm sorry, what are you referring to?

Mr. WYDEN. Well, one of the allegations, as I understood it from the report, was that they were slow to come up with programs or

initiatives to identify donors who were HIV positive. Is that correct?

Ms. CARDEN. I don't know what you're referring to.

Mr. WYDEN. All right. I was under the impression that that was one of the allegations you found. The only other point that I wanted to ask is that there is no question that a number of the matters that turn up on your inspection report relate to current procedures. Much of what we have discussed has come about in 1983, 1984, 1985, but what you are relating to are deficiencies that really stem from activities in 1989 and 1990. Is that correct?

Ms. CARDEN. That's correct.

Mr. WYDEN. OK. Well, Mr. Chairman, this has been very enlightening. We have heard information from the FDA inspectors that the 1988 agreement is not being complied with. We've got information that would suggest that this statement put out by the Red Cross a couple of days ago is simply inaccurate. And I look forward to hearing from the national office of the Red Cross as to their assessment of some of these deficiencies because I thought that 1988 agreement was to clear up some of these matters and it's quite clear that they're ongoing.

Mr. DINGELL. The Chair shares the view of the gentleman. The counsel for the minority.

Mr. MONTGOMERY. Thank you, Mr. Chairman. Mr. Bliley has requested that a series of written questions be submitted for the record.

Mr. DINGELL. Without objection, the record will kept open for the response to those questions and for the insertion of the questions themselves. Now, Ms. Carden, Mr. Smith, the committee thanks you for your assistance to us. I believe you have done an outstanding job here in carrying out your responsibilities. The Chair wants to observe that from time to time the Chair does have some harsh to say to and about the Food and Drug Administration and the Department of Health and Human Services. Certainly you have shown an example of dedicated, decent and competent service which merits the approval of the committee and the commendations of the committee.

I would like to commend you both for what it is that you have done and also the way in which you have done it. We believe that you have not only been helpful to us in your testimony today, but also you have been helpful to us in knowing what the facts and circumstances might be and in taking steps will lead to an overall improvement, not only in the regulatory actions of the Food and Drug Administration, the behavior of the American Red Cross, and others in the blood collection business, but also that you have given us the basis for appropriate action by this committee which will be the subject of considerable activity on the part of the staff of the subcommittee and the members, and also ultimately on the part of the full committee.

We intend to see to it that we first gather the facts, and second of all, to see to it that proper remedies, private, administrative and statutory, are taken vigorously. Ms. Carden and Mr. Smith, we thank you for your assistance to us. The Chair announces that if there's no further business to come before the committee, that the

committee will stand adjourned until the call of the Chair, at which time we will continue these proceedings. Thank you.

[Whereupon, at 3:30 p.m., the hearing was adjourned.]

[The following responses to subcommittee questions were received:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 24 1990

The Honorable John D. Dingell
Chairman, Subcommittee on Oversight
and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

This is in response to your letter of July 18, 1990 in which you requested written responses to questions for Food and Drug Administration (FDA) Inspector Mary Carden posed by Congressman Bliley to complete the record of the Subcommittee's July 13, 1990 hearing on the safety of the blood supply.

Enclosed are responses to those questions which were prepared by Ms. Carden. Since these questions were directed specifically to Ms. Carden, they reflect her personal opinion and understanding of the issues which have been raised and not necessarily the position of the Agency.

We would also like to provide additional comments for purposes of clarification. It should be pointed out with regard to question number one, that Form FDA 483 (Inspectional Observations), which is indeed releasable to the public, represents observations made by the investigator and is issued to the firm at the conclusion of the inspection to assist the inspected establishment in complying with FDA laws and regulations.

This list of observations does not, however, represent the official conclusions of the Agency but rather, along with the complete written report of the inspection, form the basis upon which a determination can be made relative to whether or not violations of the law have actually occurred. Please be assured that if, after review and analysis of these reports it is determined that a firm is violative, appropriate regulatory action is taken.

In addition, with regard to the 228 transfusion-associated AIDS (TAA) cases, it is not possible to make any definitive statements regarding the cases discussed in Ms. Carden's report until the review of the full inspection report, as well as other outstanding report(s) of investigation(s), is completed. Any additional follow-up of these TAA cases at other American Red Cross centers is contingent upon the continuing evaluation by our field and headquarters offices.

We hope that these responses and comments will provide some perspective on this complex issue. If we can be of any further assistance, please let us know.

Sincerely yours,

for Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date August 7, 1990

From Mary T. Carden, Investigator, IPTSB

Subject Response to Questions from Subcommittee on Oversight and Investigation of the Committee on Energy and Commerce

To Richard Klug, Director IPTSB

Question #1

Do you agree with the Washington Post's statement that "Preliminary FDA inspector's reports are not released to the public because they contain only the observations of individual agency inspectors and not official conclusions"?

Answer

The preliminary report referred to in the Washington Post is an FD 483, List of Observations. This document is routinely issued at the close of any FDA inspection in which objectionable conditions are noted. These reports are available for release to the public the day the FD 483 is issued to the firm in accordance with the Freedom of Information Act. The FD 483 does contain official conclusions by the investigator as to the non compliance of the firm being inspected. The investigator being on the scene is in the best position in the agency to make such judgements. Only significant deviations are listed and based on the judgement of the investigator the conditions are objectionable in view of their relationship to other conditions or controls at the given time or place. Following further review, the agency may later chcose not to take regulatory action even though a violation of the law exists.

Question #2

Do you agree with the Washington Post's statement that according to FDA officials, "The Red Cross was not required to report to Federal health officials cases of HIV infection from blood transfusions, but rather that responsibility lay with the individual's doctor.

Answer

I do not agree with the Washington Post's statement. An individual's physician may report a suspect HIV infection to the CDC, however, my understanding is, this is a voluntary rather than a regulatory requirement. As an FDA Investigator I am responsible for regulating the manufacture of blood products. If a blood bank receives information from a hospital or physician that a blood product they manufactured was transfused to a

recipient, who is now HIV infected, the blood bank has a responsibility to investigate the potential that an error or accident has occurred in the manufacture of the blood product. If upon investigation, the blood bank determines that an error occurred in the manufacture of the blood product, the blood bank would be required by FDA regulations to maintain records of the investigation and to report the error to FDA.

During the course of the investigation the blood bank may not be able to identify an error in the manufacturing of the blood product. In this case, if the recipient of the blood product was HIV infected and another source of the infection cannot be identified, the incident should be reported to FDA as an accident. American Red Cross's own definition of an accident states in part: an accident is an occurrence not traceable to a deviation from the CFR (Code of Federal Regulation), BSD (Blood Service Directive), or Regional SOP (Standard Operating Procedure) which affects the safety, purity, potency, or effectiveness of a blood product. Certainly products which potentially cause HIV infection in the recipient are reportable as accidents.

American Red Cross's own written procedures referred to as BSD's (Blood Service Directives) require reporting errors and accidents to FDA. Because ARC holds a U.S. license these BSD's are submitted to FDA for approval. The BSD for reporting of errors and accidents specifically states ARC will "report cases in which AIDS, septicemia, or other diseases rarely associated with transfusion were possibly transmitted".

The blood banking industry, sensitive to the potential for litigation in these cases, is very unwilling to share this information with the agency. As an investigator I need to assure blood banks are submitting the information to FDA as it is needed to effectively regulate blood products. A magazine article supplied by American Red Cross during the inspection suggests transfusion-associated HIV transmission was essentially eliminated when the HIV antibody screening test was added in March 1985. I believe it is under reported.

Question #3

Is it true, as the Washington Post reported, that the alleged deficiencies in reporting transfusion-associated AIDS cases "were not in any way responsible for those 228 HIV infections... almost all of the local infections from donated blood occurred before 1985, when antibody tests for the AIDS virus were introduced"?

Answer

The article states deficiencies in Red Cross procedures were not in any way responsible for the HIV infections... almost all of the local infections from donated blood occurred before 1985, when antibody tests for the AIDS virus were introduced"?

At the time the inspection of the National ARC was conducted, American Red Cross was unaware of the number let alone the status of any investigation into transfusion associated AIDS cases in the Washington Region. There is no basis

for the statement American Red Cross procedures were in no way responsible for the 228 HIV infections. In order to make this determination a complete investigation of all of the HIV test records and deferral status of the donor would have to be conducted. In some instances because of record discrepancies proper investigations cannot be conducted and they may be unable to draw conclusions, since all records relevant to some donors are not available.

As to the statement that almost all of the cases occurred before 1985, we did not doubt that some of the 228 cases occurred before 1985, however, National ARC was unable to provide this information. One of the records we did review during the inspection of National ARC involved a case which occurred in 1988. It has since been determined that 16 of the 228 cases occurred since 1985 when testing for anti-HIV began. Also of importance is the fact the 228 cases in the Washington Region represent transfusion associated AIDS cases from that region alone. FDA has not examined cases from the other 53 Regions of American Red Cross.

Some transfusions which occurred prior to 1985 are being reported in 1990 as potential transfusion associated AIDS cases because of the lag time in onset of clinical symptoms of the disease. As a result of this lag time transfusion associated AIDS cases resulting in transfusions since 1985 may not be reported until well into the 1990's. Studies vary as to the incubation period for AIDS. The example of only a few does not accurately represent the problem. American Red Cross has dismissed the reports of transfusion associated AIDS cases without proper investigation. In one instance the Nashville Region was involved in a transfusion associated AIDS case in which National ARC has stated there was no fault on the part of the American Red Cross. However, the records of testing in this case were lost and one cannot conclude that the blood products were properly tested without an examination of these records.

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